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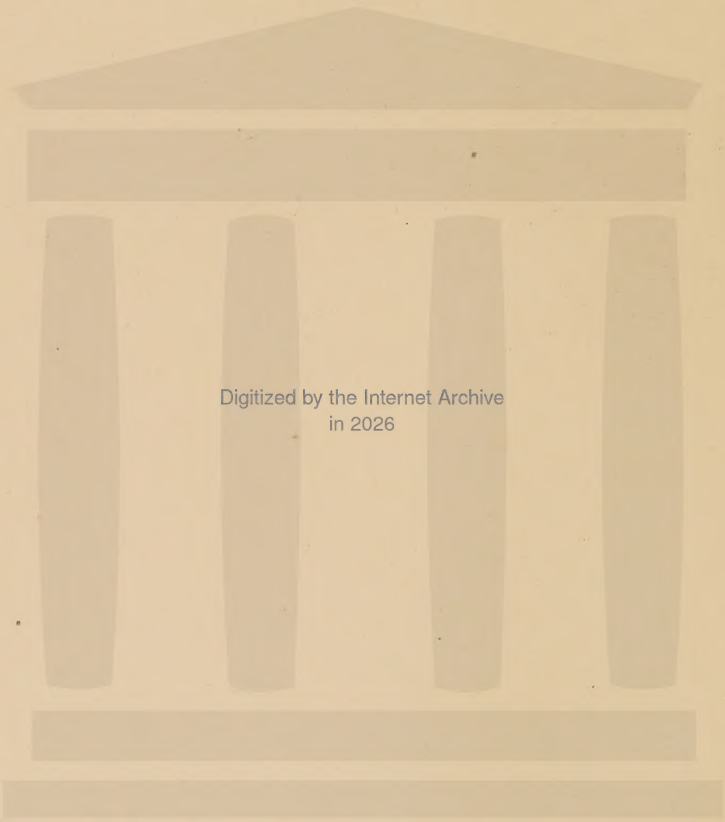
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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

TWENTY-EIGHTH SESSION

HELD AT WASHINGTON, D. C.

MAY 6, 7, AND 8, 1913

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1913

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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CONTENTS

List of Officers for the Year 1912–1913 vii
List of Officers for the Year 1913–1914 viii
List of Officers from Organization to the Present Time ix
List of Members xi
List of Associate Members xv
List of Honorary Members xvii
List of Emeritus Members. xix
List of Deceased Members xxi
Constitution xxiii
Minutes of the Twenty-eighth Annual Meeting xxvii

Address of the President. On the Cultivation of the Clinical Sciences of Diagnosis and Therapy. By Lewellys F. Barker, M.D. . . . 1
Studies on the Nature of Biological Specificity. By Frederick P. Gay, M.D. 13
The Functions of the Diaphragm and Their Diagnostic Significance. By C. F. Hoover, M.D 16
The Action of Intravenous Injections of Various Substances in Animal and Human Cancer. By Leo Loeb, M.D., M. S. Fleisher, M.D., H. N. Lyon, M.D., C. B. McClurg, M.D., and W. O. Sweek, M.D. 30
Observations on the Pasteurization of Milk. By W. W. Ford, M.D., and J. C. Pryor, M.D. 40
A Clinic for Precautionary *X*-ray Examinations. By Francis H. Williams, M.D., and Samuel W. Ellsworth, M.D. 44
On the Removal of Diffusible Substances from the Circulating Blood by Means of Dialysis. By John J. Abel, M.D., L. G. Rowntree, M.D., and B. B. Turner, M.D. 51
Experiments on the Cultivation of the Microörganism Causing Epidemic Poliomyelitis. By Simon Flexner, M.D., and Hideyo Noguchi, M.D. 55
The Mode of Transmission of Poliomyelitis. By M. J. Rosenau, M.D. 69
The Problem of Typhus Fever in the United States. By John F. Anderson, M.D. 81
The Possible Relationship of Organic Diseases of the Nervous System to Rigg's Disease. By Joseph Collins, M.D. 87

Is Serum Anaphylaxis a Danger of Sufficient Importance to Limit our Use of Protective Sera in the Treatment or Prevention of Disease? By William H. Park, M.D. 95
Spontaneous Rupture of the Spleen in Typhoid Fever; with Report of a Case Cured by Operation. By Lewis A. Conner, M.D., and William A. Downes, M.D. 103
Disseminated Miliary Tuberculosis of Lungs and Skin. By W. P. Northrup, M.D. 117
Factors Which may be Concerned in Causing Hypertrophy of the Thyroid Gland, and the Effect of Excision of this Organ upon Other of the Ductless Glands. By William Stewart Halsted, M.D. . . . 127
The Etiology, Symptomatology, Diagnosis, and Treatment of Acquired Displacement and Fixation of the Stomach and Intestines. By Thomas R. Brown, M.D. 136
On the Value of *X*-ray Examinations in the Dignosis of Ulcer of the Stomach and Duodenum. By Julius Friedenwald, M.D., and F. H. Baetjer, M.D. 157
Tests for Hepatic Function and Disease under Experimental Conditions. By G. H. Whipple, M.D., V. R. Mason, and T. C. Peightal, . . 176
An Improved Method of Dilating Esophageal Strictures. By Bertram W. Sippy, M.D. 185
The Incidence of Nephritis after Scarlet Fever. By John McCrae, M.D., M.R.C.P. 194
Further Studies of Experimental Nephritis; Some Effects of Diuretics. By Henry A. Christian, M.D. 198
Benzol in the Treatment of Leukemia. By Frank Billings, M.D. . . 202
Cultural Results in Hodgkin's Disease. By C. H. Bunting, M.D., and J. L. Yates, M.D. 226
Heredity with Reference to Carcinoma as Shown by the Study of the Cases Examined in the Pathological Laboratory of the University of Michigan during 1895–1913. By Aldred Scott Warthin, M.D., Ph.D. 235
Multiple Congenital Osteochondromas with Degeneration of Cranial Nerves and Muscular Dystrophy; Report of a Case. By Thomas R. Boggs, M.D. 248
The Diagnosis of Adherent Pericardium and the Operation of Cardiolysis. By George Dock, M.D. 254
The Treatment of Syphilitic Affections of the Central Nervous System, with Special Reference to the Use of Intraspinous Injections. By Homer F. Swift, M.D., and Arthur W. M. Ellis, M.B. . . . 258
Concerning the Etiology of Hypertrophic Pulmonary Osteoarthropathy, with a Report of Five Additional Cases. By Harlow Brooks, M.D. 275
The Diagnosis of Pulmonary Abscess. By George W. Norris, M.D., and H. R. M. Landis, M.D. 302
The Clinical Features of Cases of Subacute Bacterial Endocarditis that have Spontaneously Become Bacteria-free. By E. Libman, M.D. . 309
A Clinical Study of Hypertensive Cardiovascular Disease. By Theodore C. Janeway, M.D. 333

A Study of the Uric Acid in the Blood in Gout by the Method of Folin and Denis. By Joseph H. Pratt, M.D. 387
On the Mechanism of the Circulatory Failure in Diphtheria. By W. G. MacCallum, M.D. 399
Secondary Tumors of the Lung and Pleura. By James B. Herrick, M.D. 407
Primary Infection with Tubercle Bacilli, with Special Reference to the Thoracic Glands. By Philip King Brown, M.D. 408
A Case of Recurrent Pneumonia. By W. F. Hamilton, M.D., and A. D. Campbell, M.D. 422
On a Lobar Form of Bronchopneumonia of Long Duration, Occurring in Children and Young Adults. By David Riesman, M.D. . . . 430
The Uncertainties of the Treatment of Pulmonary Tuberculosis by Artificial Pneumothorax; Report of a Fatal Case, with Autopsy. By Lawrason Brown, M.D., and Allen K Krause, M.D. . . . 441
Thrombosis and Occlusion of Lymphatics. By Eugene L. Opie, M.D. . 449
Antityphoid Vaccination in the Army. By Major Frederick F. Russel, Medical Corps, U. S. Army. 457
Studies in Diabetic Acidosis. By A. I. Ringer, M.D. 469
Pneumonic Hemiplegias. By Chartes F. Withington, M.D. . . . 477
Venous Blood-pressure as Influenced by the Drugs Employed in Cardiovascular Therapy. By Joseph A. Capps, M.D., and S. A. Matthews, M.D. 496
Cirrhosis of the Liver Produced by Chronic Protein Intoxication. By Warfield T. Longcope, M.D. 497
On Certain of the Broader Issues of the Psychoanalytic Movement. By James J. Putnam, M.D. 513
The Psychopathology of a Case of Phobia; a Clinical Study. By Morton Prince, M.D. 530
Disturbances of the Heart-beat in the Dog Caused by Serum Anaphylaxis. By G. Canby Robinson, M.D., and John Auer, M.D. 545
Abscess of the Liver following Typhoid Fever. By Robert B. Preble, M.D. 572
The Pathology of the Thyroid in Exophthalmic Goitre. By Louis B. Wilson, M.D. 576
The Clinical and Pathological Relationship of Simple and Exophthalmic Goitre. By H. S. Plummer, M.D. 587
A Demonstration of a Depressor Substance in the Serum of the Blood of Patients Affected with Exophthalmic Goitre. By J. M. Blackford, M.D., and A. H. Sanford, M.D. 595
Report of Studies on Pneumonia. By Rufus Cole, M.D., and A. R. Dochez, M.D. 606
Urobilin: its Clinical Significance. By Ray Lyman Wilbur, M.D., and Thomas Addis, M.D. 617
A Discussion of the Manner in which Cerebral Malaria is Produced. By C. C. Bass, M.D. 683
Bleeding in Typhoid Fever. By Robert D. Rudolf, M.D. (Edin.), F.R.C.P. 686
Dental Sepsis: its Relation to the System. By C. N. B. Camac, M.D. . 700

The Colloidal Gold Reaction in the Diagnosis of Syphilitic and Other Lesions of the Cerebrospinal Nervous System. By Bertram W. Sippy, M.D., and A. M. Moody, M.D. 720
On Some Angioneural Arthroses (Periarthroses, Pararthroses) Commonly Mistaken for Gout or Rheumatism. By Solomon Solis Cohen, M.D. 739
The Etiology and Pathogenesis of Bronchiectasis. By C. P. Howard, M.D. 758

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1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston
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1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
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1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
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1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
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1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
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1893. Dock, George, 1806 Locust St., St. Louis, Missouri.
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1901. Edwards, Arthur R., 100 State St., Chicago.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis.
*1886. Fitz, Reginald H., 18 Arlington St., Boston.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
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1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 23 West Franklin St., Baltimore.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
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1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
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1902. Kober, Geo. M., 1819 Q St. N. W., Washington, D. C.

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1913. Leathes, John B., University of Toronto, Toronto, Can.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
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1910. Lord, Frederick T., 305 Beacon St., Boston.
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1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
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1905. Macallum, A. B., University of Toronto, Toronto, Canada.
1898. Mallory, F. B., Department of Pathology, Harvard Medical School, Boston.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolf, Medical School, Johns Hopkins University Baltimore.
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1904. Richardson, Mark W., 145 State House, Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1907. Rosenau, M. J., Department of Hygiene, Harvard Medical School, Boston, Mass.
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1913. Rowntree, Leonard G., Johns Hopkins Univ., Baltimore.
1913. Southard, Elmer S., Harvard Med. School, Boston.
1911. Taussig, Albert E., Metropolitan Building, St. Louis.
1910. Wadsworth, Augustus B., 114 West 55th St., New York.
1913. White, Franklin W., 322 Marlborough St., Boston.
1913. White, Wm. Charles, Univ. of Pittsburgh, Pittsburgh, Pa
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*1886.	1912.	Osler, Wm., Oxford University, England.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore, Md.

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*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
*1886.	1907.	Delafield, Francis A., 5 West 50th St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, Rush Medical College, Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay Street Road, Boston.
*1886.	1911.	Peabody, Geo. L., Newport, R. I.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1893.	1913.	Rotch, Thomas M., 197 Commonwealth Ave., Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.

Elected Active Member	Elected Emeritus Member	
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
*1886.	1907.	Sternberg, George M., 2005 Massachusetts Ave., N. W., Washington.
*1886.	1906.	Trudeau, Edward L., Saranac Lake, N. Y.
*1886.	1912.	Tyson, James, 1506 Spruce St., Philadelphia.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge.
*1886.	1912.	Ward, Samuel B., 281 State St., Albany.
*1886.	1911.	Wilkins, George, 899 Dorchester St., Montreal.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C., 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members.

Date of Election

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
*1886. Folsom, Chas. F., Boston.
*1886. Formad, Henry F., Philadelphia.
*1886. Forchheimer, F., Cincinnati.
1889. Geddings, W. H., Aiken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, E. Darwin, Jr., New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.

Date of Election.

*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Spring, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 15, 1912

Article I

Object and Name

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II

Members

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III

Officers

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV

Duty of Officers

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V

Council

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate,

and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI

Meetings

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the Transactions as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII

Quorum

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

Article VIII

Election of Members

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting

of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX

Annual Dues

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X

Amendments to the Constitution

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

TWENTY-EIGHTH ANNUAL MEETING

Held at Washington, D. C., May 6, 7, and 8, 1913

The following members were present at the meeting:

A. C. Abbott,
J. J. Abel,
S. S. Adams,
I. Adler,
J. M. Anders,
J. F. Anderson,
J. Auer,
R. H. Babcock,
E. R. Baldwin,
L. F. Barker,
H. M. Biggs,
F. Billings,
A. D. Blackader,
T. R. Boggs,
B. M. Bolton,
C. S. Bond,
H. Brooks,
L. Brown,
P. K. Brown,
C. H. Bunting,
R. C. Cabot,
C. N. B. Camac,
J. A. Capps,
C. Cary,
H. A. Christian,
S. S. Cohen,
R. I. Cole,
W. Coleman,
J. Collins,
L. A. Conner,
W. M. L. Coplin,
C. L. Dana,
G. Dock,
A. R. Edwards,
H. C. Ernst,
J. Ewing,
F. G. Finley,
W. E. Fischel,
S. Flexner,
F. Forchheimer,
W. W. Ford,
R. G. Freeman,
J. Friedenwald,
M. H. Fussell,
F. P. Gay,
H. C. Gordinier,
J. P. C. Griffith,
H. A. Hare,
J. B. Herrick,
L. E. Holt,
C. F. Hoover,
C. P. Howard,
W. T. Howard,
J. Howland,
H. Hun,
R. Hunt,
H. Jackson,
T. C. Janeway,
J. J. Kinyoun,
O. Klotz,
G. M. Kober,
E. Libman,
E. Locke,
L. Loeb,
W. T. Longcope,
F. T. Lord,
J. McCrae,
T. McCrae,
A. McPhedran,
W. G. MacCallum,
F. B. Mallory,
C. F. Martin,

S. J. Meltzer,
A. Meyer,
J. L. Miller,
J. K. Mitchell,
J. L. Morse,
G. W. Norris,
W. P. Northrup,
E. L. Opie,
W. H. Park,
R. M. Pearce,
J. H. Pratt,
R. B. Preble,
M. Prince,
T. M. Prudden,
J. J. Putnam,
B. K. Rachford,
D. Riesman,
M. J. Rosenau,
F. F. Russell,
B. Sachs,
J. Sailer,
G. G. Sears,
H. Sewall,
B. W. Sippy,
T. B. Smith,
T. H. Sollman,
C. G. Stockton,
A. E. Taussig,
A. E. Taylor,
J. S. Thacker,
W. S. Thayer,
W. H. Thomson,
V. C. Vaughan,
V. C. Vaughan, Jr.,
A. B. Wadsworth,
A. S. Warthin,
G. H. Weaver,
W. H. Welch,
G. H. Whipple,
F. H. Williams,
H. U. Williams,
L. B. Wilson,
C. F. Withington.

Tuesday, May 6

The Association was called to order at 9 A.M. by President Barker, who delivered the President's address.

The Treasurer read his annual report, which was referred to an auditing committee consisting of Drs. Cabot and Hoover.

The Secretary presented the following recommendation from the Council:

That the annual dues for the ensuing year be as follows: Salaried laboratory workers, $5.00; practitioners, $15.00; associate members, $7.50, and that the Transactions of the Association be furnished upon application to Emeritus Members at $4.00 per volume.

Upon motion, this recommendation was adopted.

The Secretary reported that the Council recommends to the Association the election of the following officers for the ensuing year, and also the following nominees for active and associate members: *President,* Simon Flexner; *Vice-President,* S. J. Meltzer; *Secretary,* Geo. M. Kober; *Recorder,* Thomas McCrae; *Treasurer,* J. P. Crozer Griffith; *Councillor,* Herman M. Biggs.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons, W. S. Thayer; *Alternate Representative,* Theodore C. Janeway.

Active Members: Jno. F. Anderson, Washington; John Auer, New York; Thomas R. Boggs, Baltimore; Harlow Brooks, New York; C. H. Bunting, Madison; Wm. W. Ford, Baltimore; Julius Friedenwald, Baltimore; John B. Leathes, Toronto, and George H. Whipple, Baltimore.

Associate Members: Charles W. Duval, New Orleans; Louis V. Hamman, Baltimore; Henry R. M. Landis, Philadelphia; Roger S. Morris, St. Louis; G. Canby Robinson, St. Louis; Leonard G. Rowntree, Baltimore; Elmer Ernest Southard, Boston; Franklin W. White, Boston, and Wm. Charles White, Pittsburg.

The President, Dr. Barker, expressed the regret with which the Council had acceded to the withdrawal of Dr. S. Solis Cohen as Recorder.

Dr. F. P. Gay read a paper entitled "Studies on the Nature of Biological Specificity," which was discussed by Dr. V. C. Vaughan.

Dr. V. C. Vaughan read a paper entitled "The Poisonous Group in the Protein Molecule," which was not discussed.

Dr. C. F. Hoover read a paper entitled "The Functions of the Diaphragm," which was discussed by Dr. Conner, Dr. Hoover closing the discussion.

Dr. Leo Loeb presented "Observations on the Treatment of Human and Animal Cancer by the Intravenous Injection of Various Substances," which was not discussed.

Dr. W. W. Ford presented "Observations on the Pasteurization of Milk," which was discussed by Drs. Park and Rosenau, Dr. Ford closing the discussion.

Dr. Francis H. Williams presented a communication entitled "A Clinic for Precautionary *X*-ray Examinations," which was discussed by Drs. Cabot and Conner, the discussion being closed by Dr. Williams.

Dr. J. Abel presented a communication "On the Removal of Diffusible Substances from the Blood of Living Animals by Dialysis," which was discussed by Drs. Billings and Meltzer.

Dr. W. H. Park read a paper entitled "The Importance of Anaphylactic Phenomena and the Means of Lessening them by Refining the Serum or Desensitizing the Patient," which was discussed by Drs. Flexner, Billings, Withington, Meltzer, Anderson, and Kinyoun, the discussion being closed by Dr. Park.

Dr. Simon Flexner presented a "Communication on the Cultivation of the Virus of Poliomyelitis," which was discussed by Drs. Park, Rosenau, and Billings, Dr. Flexner closing the discussion.

Dr. M. J. Rosenau read a paper on "Transmission of Poliomyelitis," which was discussed by Dr. Flexner.

Dr. J. F. Anderson read a paper entitled "The Problem of Typhus Fever in the United States," which was discussed by Drs. W. H. Thomson, Park, Conner, and Biggs, Dr. Anderson closing the discussion.

Dr. Theobald Smith read a paper entitled "A Paratyphoid Bacillus (from fowls) and its Toxins," which was discussed by Drs. Park and Vaughan, the discussion being closed by Dr. Smith.

Dr. Lewis A. Conner reported a case of "Rupture of the Spleen in Typhoid Fever (with cure by operation)," which was discussed by Dr. Janeway.

Dr. Joseph Collins read a paper entitled "The Possible Relationship between Rigg's Disease and Organic Disease of the Nervous System," which was discussed by Drs. Ford, Billings, Lord, Bond, and Conner, Dr. Collins closing the discussion.

Dr. W. P. Northrup reported "Three Cases of General Disseminated Miliary Tuberculosis Involving the Skin," which communication was discussed by Dr. Solis Cohen, the discussion being closed by Dr. Northrup.

Adjourned at 1.15 P.M.

Wednesday, May 7

Morning Session.—The Association was called to order by President Barker at 9.15 A.M.

Dr. W. S. Halsted, by invitation, read a paper entitled "Some of the Causes of Experimental Hyperplasia of the Thyroid Gland,"

which was discussed by Drs. Meltzer and MacCallum, the discussion being closed by Dr. Halsted.

Dr. L. B. Wilson read a paper entitled "The Pathology of the Thyroid Gland in Exophthalmic Goitre."

Dr. H. S. Plummer, by invitation, read a paper entitled "The Clinical Differentiation of the Various Types of Goitre."

Dr. J. M. Blackford, by invitation, read a paper entitled "The Effects on Blood Pressure of the Injection of Thyroid and Other Extracts."

The foregoing three papers were discussed jointly by Drs. Meltzer, Vaughan, Billings, Whipple, Ochsner, and Cabot, the discussion being closed by Drs. Wilson, Plummer, and Blackford.

Dr. T. R. Brown read a paper entitled "The Etiology, Symptomatology, Diagnosis, and Treatment of Acquired Displacements of the Stomach and Intestines," which was discussed by Drs. Cabot and Meltzer, Dr. Brown closing the discussion.

Dr. A. I. Ringer, by invitation, read a paper entitled "On the Combustion of Fat in Diabetes," which was discussed by Drs. Janeway and Leathes, the discussion being closed by Dr. Ringer.

Drs. J. Friedenwald and F. H. Baetjer read papers on "The *X*-ray Diagnosis of Ulcer of the Stomach and Duodenum," which were discussed by Drs. Meltzer, Fussell, Thayer, and Solis Cohen, the discussion being closed by Drs. Friedenwald and Baetjer.

Dr. G. H. Whipple read a paper entitled "Tests for Hepatic Function under Experimental Conditions," which was discussed by Dr. Taylor, Dr. Whipple closing the discussion.

Dr. B. W. Sippy presented "An Improved Method of Dilating Organic Strictures of the Esophagus," and demonstrated the method on a patient. The communication was discussed by Drs. Plummer and Meltzer, Dr. Sippy closing the discussion.

Dr. S. Solis Cohen presented a communication on "Some Angioneural Arthroses Commonly Mistaken for Gout and Rheumatism," which was not discussed.

Dr. John McCrae read a paper entitled "Scarlet Fever and Nephritis," which was discussed by Drs. Thayer and Miller, Dr. McCrae closing the discussion.

Dr. H. A. Christian presented "Further Studies of Experimental Nephritis," which communication was discussed by Drs. Miller and Solis Cohen, the discussion being closed by Dr. Christian.

Dr. Frank Billings read a paper entitled "The Benzol Treatment of Leukemia," which was discussed by Drs. Cabot, Miller, Herrick, Tyson, and McPhedran, the discussion being closed by Dr. Billings.

Drs. C. H. Bunting and J. L. Yates presented "A Report of Cultural Investigation of Hodgkin's Disease."

Dr. C. H. Bunting also read a paper entitled "The Value of the Differential Leukocyte Count in Diagnosis of Glandular Enlargements," which were not discussed.

Dr. J. H. Pratt read a paper entitled "Some Clinical Applications of Folin's New Method of Blood Analysis," which was discussed by Drs. Cohen, Pearce, and Libman, Dr. Pratt closing the discussion

The Association then proceeded to the election of officers, active members, and associate members, with the following result:

President, Simon Flexner.

Vice-President, S. J. Meltzer.

Secretary, Geo. M. Kober.

Recorder, Thomas McCrae.

Treasurer, J. P. Crozer Griffith.

Councillor, Herman M. Biggs.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons, W. S. Thayer.

Alternate Representative, Theodore C. Janeway.

Active Members: Jno. F. Anderson, Washington; John Auer, New York; Thomas R. Boggs, Baltimore; Harlow Brooks, New York; C. H. Bunting, Madison; Wm. W. Ford, Baltimore; Julius Friedenwald, Baltimore; John B. Leathes, Toronto, and George H. Whipple, Baltimore.

Associate Members: Charles W. Duval, New Orleans; Louis V. Hamman, Baltimore; Henry R. M. Landis, Philadelphia; Roger S. Morris, St. Louis; G. Canby Robinson, St. Louis; Leonard G. Rowntree, Baltimore; Elmer Ernest Southard, Boston; Franklin W. White, Boston, and Wm. Charles White, Pittsburgh.

Adjourned at 1.20 P.M

Evening Session.—The Association was called to order by President Barker at 9.00 P.M.

Dr. A. S. Warthin presented a communication on "Heredity with Reference to Neoplasm as Shown by a Study of 3000 Cases Examined in the Pathological Laboratory at the University of Michigan during the Years from 1895 to 1913," which was not discussed.

Dr. T. R. Boggs reported a case of "Multiple Congenital Exostoses, with Dystrophic Changes and Cranial Nerve Atrophy," which was discussed by Dr. Cole, Dr. Boggs closing the discussion.

Drs. John Auer and G. Canby Robinson presented a communication entitled "Disturbances of the Heart Beat in the Dog Caused by Serum Anaphylaxis," which was discussed by Dr. W. G. MacCallum, Dr. Auer closing the discussion.

Major F. F. Russell, United States Army, read a paper entitled "What has been Accomplished with Antityphoid Vaccination in the Army," which was discussed by Drs. Abbott, Park, Thayer, Kober, Vaughan, Fussell, Dock, and T. McCrae, the discussion being closed by Dr. Russell.

Dr. George Dock presented a communication "On the Diagnosis and Treatment of Mediastinopericarditis," which was discussed by Dr. McPhedran, Dr. Dock closing the discussion.

Dr. H. F. Swift, by invitation, read a paper entitled "The Treatment of Cerebrospinal Syphilis by Intraspinous Injections," which was discussed by Drs. Hoover and Meltzer, the discussion being closed by Dr. Swift.

All of the foregoing papers were illustrated by Lantern Slides.

Adjourned at 11 P.M.

THURSDAY, MAY 8.

The Association was called to order by President Barker at 9 A.M.

Dr. Harlow Brooks read a paper entitled "Hypertrophic Pulmonary Osteoarthropathy," which was not discussed.

Dr. G. W. Norris read a paper entitled "The Diagnosis of Pulmonary Abscess," which was discussed by Drs. Fussell, Libman,

Dock, Lord, and P. K. Brown, the discussion being closed by Dr. Norris.

Dr. E. Libman read a paper entitled "The Clinical Features of Cases of Subacute Bacterial Endocarditis that Have Spontaneously become Bacteria-free," which was discussed by Dr. Sewall, Dr. Libman closing the discussion.

Dr. George Dock exhibited a specimen illustrative of his paper on Mediastinopericarditis.

Dr. George Dock exhibited for Dr. Hugh McCulloch, of St. Louis, a specimen of Tenia Saginata with Y-shaped Proglottides, which was discussed by Dr. W. G. MacCallum, the discussion being closed by Dr. Dock.

Dr. T. C. Janeway presented "A Clinical Study of Hypertensive Cardiovascular Disease," which was discussed by Drs. Cabot, Sewall, Miller, Thayer, Jackson, Hoover, and McPhedran, the discussion being closed by Dr. Janeway.

Dr. E. L. Opie read a paper entitled "Thrombosis of the Thoracic Duct," which was not discussed.

Dr. W. G. MacCallum read a paper entitled "The Effect of Diphtheria Poisoning on the Circulation," which was discussed by Dr. Meltzer, Dr. MacCallum closing the discussion.

Dr. J. B. Herrick presented a communication on "Secondary Tumors of the Lung and Pleura," which was not discussed.

Dr. P. K. Brown read a paper entitled "The Infection of the Bronchial Glands and their Relation to the Processes in the Lungs," which was discussed by Dr. Theobald Smith, Dr. Brown closing the discussion.

Drs. R. I. Cole and A. R. Dochez presented a "Report of Studies on Pneumonia," which was discussed by Drs. Vaughan and Bond, the discussion being closed by Dr. Cole.

Dr. W. F. Hamilton presented a communication "On Recurrent Pneumonia," which was not discussed.

Dr. David Riesman presented a communication "On a Lobar Form of Bronchopneumonia of Long Duration, Occurring in Children and Young Adults," which was discussed by Drs. Cabot, Meltzer, Lord, Miller, and J. B. Leathes, Dr. Riesman closing the discussion.

Dr. C. P. Howard read a paper entitled "The Etiology and Pathogenesis of Bronchiectasis," which was discussed by Drs. Lord, W. G. MacCallum, Meltzer, Capps, and Hoover, the discussion being closed by Dr. Howard.

Drs. Lawrason Brown and A. K. Krause presented a communication on "Artificial Pneumothorax," which was discussed by Drs. Lord and W. G. MacCallum, Dr. Brown closing the discussion.

Dr. V. C. Vaughan, Jr., read a paper entitled "The Present Status of the Treatment of Pulmonary Hemorrhage," which was discussed by Dr. Fussell, Dr. Vaughan closing the discussion.

Dr. C. C. Bass, by invitation, read a paper entitled "A Discussion of Cerebral Malaria in the Light of Recent Observations," which was not discussed.

Dr. B. W. Sippy read a paper entitled "The Colloidal Gold Reaction in the Diagnosis of Syphilitic and Other Lesions of the Cerebrospinal Nervous System," which was discussed by Drs. Cabot and Hoover, Dr. Sippy closing the discussion.

Dr. C. F. Withington presented a communication on "Pneumonic Hemiplegias," which was discussed by Dr. Capps, Dr. Withington closing the discussion.

The following papers were read by title:

"Effect of Cardiovascular Stimulants on the Venous Blood Pressure," by Dr. J. A. Capps.

"The Relation of Dental to Systemic Sepsis," by Dr. C. N. B. Camac.

"Observations upon the Metabolism of Oatmeal in Diabetes Mellitus," by Dr. E. P. Joslin.

"Experimental Cirrhosis of the Liver," by Dr. W. T. Longcope.

"The Clinical Significance of Urobilin," by Drs. R. L. Wilbur and Addis.

"The Influence of Diet and of Volume of Urine upon Urinary Acidity," by Dr. A. E. Taylor.

"Erythemia, with Chronic Cyanosis and Splenomegaly," by Dr. C. L. Greene.

"Comments on the Broader Issues of the Psychoanalytic Movement," by Dr. J. J. Putnam.

"A Clinical Study of a Case of Phobia," by Dr. Morton Prince.

"Bleeding in Typhoid Fever," by Dr. R. D. Rudolf.

"Abscess of the Liver following Typhoid Fever," by Dr. R. B. Preble.

Dr. Cabot, for the Auditing Committee, reported that the Treasurer's accounts had been examined and found to be correct.

The Secretary presented a recommendation from the Council, that Drs. Thomas Mitchell Prudden and William Henry Welch be elected to Honorary Membership. Upon motion of Dr. Meltzer, seconded by Dr. Thayer, the Secretary was instructed to cast the unanimous vote of the Association for Drs. Thomas Mitchell Prudden and William Henry Welch as Honorary Members of the Association.

The Secretary announced the receipt of a letter from Dr. W. W. Keen requesting the coöperation of the Association in securing subscriptions to the "Lister International Memorial Fund," which request the Council recommends to the favorable consideration of the individual members.

Upon motion of Dr. V. C. Vaughan a rising vote of thanks was tendered to President Lewellys F. Barker for the preparation of a program of unusual interest and importance.

Adjourned at 1.20 P.M

GEORGE M. KOBER,
Secretary.

ADDRESS OF THE PRESIDENT

ON THE CULTIVATION OF THE CLINICAL SCIENCES OF DIAGNOSIS AND THERAPY

By LEWELLYS F. BARKER, M.D.
BALTIMORE

In preparing this address some weeks ago, I had written the statement that the membership of this Association had fortunately been spared by death from any diminution in its numbers during the past year; shortly before this meeting, however, the association has suffered the loss of two of its original members—Dr. John S. Billings and Dr. Francis P. Kinnicutt, and one of its associate members, Dr. Hugh A. Stewart.

We now enter upon the work of the twenty-eighth annual meeting. Each annual session begins with an address from the President, by by-law limited to half an hour, and by custom including (1) an expression of appreciation of the honor of presiding over the assembly, and (2) suggestions for the promotion of the welfare of the Association and, more especially for the adaptation of its functions to the ever-changing conditions of American medicine.

My first duty is, then, to give thanks. The President of the Association would indeed be guilty of ingratitude were he to omit to thank his colleagues for the honor and distinction they confer upon him by his election. Even though the choice comes automatically in serial sequence to members of the council, to be chosen as this officer is an honor which an ambitious physician might well be willing to look forward to as a possible culminating event

in a life of distinguished service in the profession. In the present instance, the selection has obviously been made rather as an encouragement to future work than as a reward for past performance; I can only be grateful for the generosity shown me and for the powerful stimulus to worthy effort which such confidence begets.

Turning now to the work of the Association itself, it is plain that the great changes which have taken place in medicine since the foundation of the society in 1886, have modified old needs as regards associations and created new ones. Our attention has been called repeatedly to the changing needs by our presiding officers, most emphatically, perhaps, by Dr. Councilman in 1904, and by Dr. Adami last year.

Methods of medical education in the United States have passed through a veritable revolution. The proprietary medical schools, useful enough in their time, became insufficient and have been largely replaced by medical departments of universities, privately endowed, or aided by the States. The laboratory disciplines, under the stimulus of the great advances of biology, chemistry, and physics in the second half of the last century, have experienced an unprecedented expansion, and the army of medical teachers and investigators has thus been recruited by a series of new battalions, made up of men trained in pathology, bacteriology, physiology, psychology, physiological chemistry, pharmacology, anatomy, histology, and embryology. Many of the teachers and investigators in these purely laboratory branches are men limited in clinical experience to their undergraduate training, some of them, indeed, have entered upon a career in these fundamental medical sciences, after a preliminary apprenticeship in laboratories of biology or chemistry without taking even an undergraduate course in medicine. Meantime a high degree of specialization has been taking place also in the clinical branches. With the advent of anesthesia and asepsis in surgery came the opportunity for unexpected divisions of labor in surgical fields, while the introduction of instruments of precision, and of the methods of pathology and bacteriology, of biology and chemistry, in the work of internal medicine led to the intensive development, by skilled workers, of its various special domains.

One result of the almost explosive progress in the purely laboratory branches, has been to place the clinical subjects, and especially internal medicine, in almost an embarrassing situation. Internal medicine is, of all the biological sciences, the one to which the largest number of other sciences contribute facts for application. Internal medicine is usually designated as one of the "applied sciences." But all the sciences, with the possible exception of mathematics, are largely "applied science." Thus, physics consists in part of applications of mathematics; chemistry of applications of mathematics and physics; biology of mathematics, physics, and chemistry; physiology of physics, chemistry and biology, and so on, with avalanche-like increase of the sciences to be applied, until internal medicine is reached with all the laboratory subjects offering it their aid.

Now each of these sciences, though largely applied science, is compelled to grow in its own way; each science is creative and has to devise methods of its own; even when a new fact in a science basal to it is applicable, the application has actually to be made. Take physiology as an example. A new discovery in physics or in chemistry does not enrich physiology until physiology makes use of it; indeed, it may long lie unapplied since its fruitful application in physiology involves a physiological research. The number of physical, chemical, and biological facts as yet unapplied to physiological problems is so enormous, and the number and powers of physiological workers relatively so limited, that progress, though rapid, in physiology can by no means keep pace with that of its underlying sciences, no matter how desirable this may seem.

The clinical subjects are similarly situated though in transcendent degree. It is almost a wonder that the clinician is not suffocated by the physical, chemical, biological, anatomical, physiological, pharmacological, pathological, parasitological, and psychological facts which are being heaped upon him with clamor for their application. Moreover, the facts have arrived so suddenly that they find the clinician, in many instances, unable to understand them, much less to apply them. Certain chemical, physiological, and anatomical facts the clinician of the last generation, had, indeed, trained himself to apply by study in the postmortem room, in the

histological laboratory, and in the laboratory for urinalysis. But recently, and all at once, the air has become thick with applicable facts of the most diverse origin, and only the younger clincians have had opportunity for securing a training permitting of an understanding of even a part of them.

For some years past, students have been entering the clinics for instruction after three or four years of education in the methods and facts of the basal sciences from physics to pathology. They have been surprised to find, in many instances, their clinical teachers relatively unacquainted with the present-day content of the laboratory disciplines, and have often been astonished at the delay in attempting to apply in clinical studies facts of those laboratory branches which seem to them obviously applicable to the work of diagnosis and therapy. Such personal observations by students working in the clinics have been a sharp spur to clinical men, and have undoubtedly gone far toward accelerating the application of laboratory facts and methods in the study and treatment of the sick. At times, of course, criticisms have been too severe or unjust. Students are prone to be harsh critics; their "young hot blood tingles to be up and doing;" often they know little of the circumstances which delay progress. In certain regrettable instances students may even have been led by a zealous but ill-informed pre-clinical teacher to believe that the workers in the clinical branches are not to be regarded as "scientific," but rather as "merely practical" men. This is an attitude occasionally assumed —happily less often now than a few years ago—by representatives of various sciences to all sciences to which they contribute facts for application, that is, to all sciences except those which are basal to their own. I can recall the time when an occasional teacher of physics, or of chemistry, hinted that the representatives of physiology or of physiological chemistry were amateurish or unscientific because the work in these branches is subject to conditions often inconsonant with profitable measurement in dynes or with graphic representation of stereochemical conceptions. But the older may well profit from the criticism of the younger, even if it be arrogant or unjust. The veteran, when taken to task by the recruit, may be amused, but if wise, instead of being offended, he will listen and

will try to rejuvenate himself. In any case, he will rejoice in the vigor and optimism of the youth, and a part of his reward will lie in the consciousness of helping to train a group of successors who will surpass him.

It has been interesting to observe the attempts which have recently been made more fully and rapidly to utilize the new knowledge in the underlying sciences for the furthering of the work of diagnosis and therapy in the clinics. On the one hand, the older clinicians have heroically endeavored to acquaint themselves with the new facts as they have appeared; and they have hastened to surround themselves in their wards and in the clinical laboratories with younger men, trained in the newer laboratory methods, men who could aid them in the work of clinically applying the new facts. And, on the other hand, several universities have recently appointed to important clinical positions men who have been trained predominantly in the laboratory branches and who have made their early reputation in pathology, physiology, anatomy, or chemistry, rather than in the clinical sciences. In these instances, we see two methods used to overcome a great difficulty and both are laudable. Each of them has led to advances in clinical teaching and research, but each of them is subject to obvious disadvantages. In the one instance, the clinical problems may be in the foreground, but insufficient personal acquantance with the newer fundamental facts to be utilized limits vision; moreover, the lack of machinery for the utilization of the newer knowledge hampers the organization of diagnostic and therapeutic investigation. In the other instance, there is a real danger of an under-appreciation of the nature, significance, and scientific importance of the problems of diagnosis and therapeusis as such; the clinical appointee, especially when untrained, or only slightly trained, in clinical work, and previously nursed in a fosterage perhaps unfamiliar with, or even mildly disparaging of the work of the clinic and of clinicians, may feel actually ashamed to work at the bedside and in the laboratory at truly clinical problems, feeling that his former colleagues, to whom he may owe his appointment, will regard him as a scientific clinician only when he avoids researches bearing directly upon diagnosis and therapy and devotes his energies to the solution of non-clinical

problems, the attack on which properly belongs to the laboratories of pathology, physiology, or chemistry.

The situation is gradually righting itself. The non-clinical scientists realize better than they did what clinical work is and should be, and that workers in clinical branches should not be expected to leave their own fields to conduct other researches any more than the clinician can expect the anatomists or the physiological chemists to solve either the diagnostic and therapeutic problems of the clinic or the fundamental problems of physics and mathematics. All are acknowledging that the problems of diagnosis and therapy are tasks set by the patients themselves; that these living patients are, primarily, the objects of study of the clinical scientist. For this study a fine imaginative vision—properly schooled and rigidly controlled—is desirable. Patients must, in each generation, be looked at with fresh eyes, intellectualized partly by accurate training in the most recent clinical technique, partly by previous education in the methods, facts, and hypotheses of the non-clinical sciences. It is gratifying that clinical men themselves, including those with extended training in one or more of the non-clinical sciences, are, more than ever before, recognizing the worth and dignity of diagnosis and therapy as sciences *per se*—that is to say, as bodies of knowledge to be increased, not merely as arts to be practised—sciences to be cultivated for their own sake as intensively as proudly, and as enthusiastically as are the more basal sciences. And this is why clinical men are seeing to it that provision is made in the clinics themselves, not for the presence of patients only, but also for elaborate machinery for investigating them; they are demanding and equipping *in each clinic* a number of laboratories in which physical, chemical, physiological, pharmacological, bacteriological, psychological, and other methods and facts can be directly applied by trained men in the diagnostic and therapeutic inquiries to which the conditions existing in the patients actually before them lead. And, in addition to the more permanent staff, they are taking with them to the bedside and to the adjacent experimental laboratories of the clinic groups of medical students, trained in the basal medical sciences and making them responsible for the large amounts of routine work of which these students are capable while they are

acquiring their early clinical experiences. To obtain proper facilities for clinical study, and especially the multiple laboratories manned by skilled workers necessary in each clinic, not only will much money be required, but also an awakening of the understanding of the clinical men themselves, of non-clinical medical scientists, and of hospital superintendents and trustees to the need. By many it is still thought that the laboratories of the non-clinical sciences can be called upon to do the laboratory work of the clinical sciences. By others, and especially by the superintendents of general hospitals (who are forced rigidly to limit the expenditure of money), the fallacy is still cherished that a "general clinical laboratory" in the hospital can best do the work of all the clinics for them. This, it seems to me, is a grave error. I am convinced that nothing short of multiple special laboratory divisions *for the direction of which each clinic is itself actually responsible,* will ever satisfactorily supply the needs. Any other arrangement will emasculate the individual clinics and paralyze research in diagnosis and therapy. It was for a precisely similar independence for physiology that Purkinje had his great struggle about the beginning of the last century. The university faculty and the university Kurator put great obstacles in the way. They did not see why physiology should not use the other laboratory (anatomy) for the work. The Kurator sarcastically asked, "Where will it lead to if every scientific branch demands its own laboratory?" Thanks to Purkinje's clear vision and his persistence, and through the influence of Goethe and Alex. v. Humboldt, physiology finally got its independent institute. Von Ziemssen recognized a similar need for the medical clinics and demanded a "clinical institute" for teaching and laboratory researches in addition to his hospital wards.[1] Only after such salutary conditions as those referred to have been realized in the clinics, and have been maintained there for a time, can we hope to breed a generation of clinicians in any way approaching the next necessary and realizable type—a type resulting from the fusion of training in accurate clinical observation with training in the solution of clinical problems by experimental work in the laboratory. The

[1] The Organizations of the Laboratories in the Medical Clinic, Johns Hopkins Hospital Bull., 1909, xviii, 193–198.

goal stands clearly in the view of those of us who are familiar with the present conditions and are ambitious for the advance of clinical knowledge. That this goal is being rapidly approached should be a consolation to the generation of clinicians chafing under the limitations of the period through which we are passing, more than one member of which has felt keenly the truth of the adage that "the man who rings the bell cannot march in the procession."

The state of affairs to which I have referred has, to a certain extent, been reflected in the membership, and in the programs of the meetings, of this Association. In 1886 the membership was made up chiefly of clinicians with a sprinkling of laboratory workers. In 1899, of 118 members, some 18 were pure laboratory workers who saw no patients at all. At present of 131 members, some 32 are pure laboratory workers who do not see patients, and many more are largely engaged in experimental work. Of the associate members, from whom our new members are in the near future to be drawn, at least one-third are men who do not study patients but are engaged entirely in laboratory teaching or research.

A glance over the program of the meeting of 1899, shows that three non-clinical and twenty-seven clinical papers were presented. Last year, the program listed some thirteen non-clinical and some forty-six clinical papers. Our program this year includes some fourteen non-clinical and some fifty-one clinical papers.[1] A large proportion of the papers classed as clinical are reports of combined bedside and laboratory work. Now, on the whole this must be regarded as a very gratifying showing, illustrating, as it does, the great expansion in our clinics of work by experimental methods, as contrasted with work by more purely observational and statistical methods.

None welcomes, nor confides in, the experimental method more, perhaps, than I, but the observational method also deserves ever new application in clinical work. Is it not conceivable that we may actually retard progress in diagnosis and therapy if we centre investigation in our clinics and in their laboratories upon problems

[1] In making this arbitrary division into clinical and non-clinical papers I am guided by the direct relationship of the topic to the diagnosis and treatment of disease in human beings.

far removed from the conditions observable in the sick? May it not be desirable to plan that the experimental work in the clinics shall, for the most part, bear directly upon the problems of diagnosis and therapy (of course, in a wide sense, including etiology, pathogenesis, and prognosis), and to arrange that the more fundamental physiological and experimental pathological inquiries be relegated to those laboratories, the particular business of which is to advance the sciences of general physiology and general pathology. Unless clinical men jealously guard their time, their interest, their energies and their materials in order to devote them to the advance of the clinical sciences, the progress of diagnosis and therapy must be slowed. Not that now and then a clinician may not become so interested in pathology, physiology, or physics as to make it justifiable for him to leave the clinic and occupy a non-clinical post. The clinics can only be proud to send occasionally a Helmholtz to physiology, as chemistry may be glad to contribute an Ostwald to philosophy. A man must go where his cerebral cortex leads him, be it from physic to physics, as in Helmholtz's case, or from crystallography to therapy as in Pasteur's. Moreover, even in truly clinical investigation there will often be non-clinical by-products of great scientific value to which there can be no objection provided the main product corresponds to the aims of the clinical sciences. But, at this time, it would seem important to emphasize that researches in general physiology and in general pathology, valuable and desirable as they are for the progress of the medical sciences, as a whole, pertain to a field other than that which the clinics themselves should predominantly cultivate. May I illustrate by an analogy? Were our physiologists to devote their time chiefly to the inquiries now pursued in the university laboratories of physics and chemistry to the neglect of their own physiological studies the science of physiology would undoubtedly suffer. Now, none the less will scientific clinical work suffer loss if the men who are presumably cultivating the clinical sciences of diagnosis and therapy overlook their own legitimate problems, neglecting their clinical material to dissipate their time, and their energies, in the general or special non-clinical inquiries which properly belong to the more fundamental laboratories. The Wassermann reaction may be

primarily worked out in a non-clinical laboratory, but the determination of its real significance for the diagnosis and treatment of disease demands, subsequently, long years of clinical research. Salvarsan may be made, and its spirillocidal power tested, in experimental non-clinical laboratories, but its application and value in the treatment of the different forms of syphilis are problems upon which the clinics have only begun to work—problems the full solution of which may be slow in following upon the initial non-clinical investigations.

And this brings me again to our membership and the programs of our meetings. The mingling of clinicians (who study patients and who do experimental work in laboratories on clinical problems) with non-clinical experimental workers is stimulating, I believe, to both and *I trust that this Association will always contain both.* Certainly, our non-clinical members have been and now are the very flower of our Association. It must be remembered, however, that the anatomists, the physiologists, the biological chemists, and the pathologists and bacteriologists now have their special societies, but that practitioners, teachers, and investigators of internal medicine have their principal prepresentation in this association, and it has always been taken for granted that this association is mainly, though not exclusively, a society for workers in internal medicine (in the broad sense). In selecting new members, ought we not always to keep this main function of the association in mind?

Again, may we not do well to pay close attention to this main function in making up the programs for our annual meetings? There is a widespread and growing feeling among our members that the farther removed a paper is from the examination and treatment of patients, the more acceptable it is for the program. Able clinical men have told me that they find some of the papers presented at the meetings too far removed from the fields of diagnosis and therapy to be interesting or even intelligible to them. "Those who read these papers speak to us as in a foreign language" is a complaint I have more than once heard. Such a difficulty cannot, of course, with a mixed membership, be wholly overcome. But something could, it seems to me, be done to remedy what

careful consideration indicates is a real detriment to the fullest success of our meetings. Better suggestions than mine will, I hope, come from other members, but two possibilities occur to me. First, might we not, while accepting some papers in general physiology and general pathology, urge that they be of a character likely to enlist the interest of clinicians and that they be presented in a form easy to understand by men who have not worked upon the special subjects with which they deal; papers in general pathology and physiology of different content might better be presented in the societies of the physiologists and pathologists. Secondly, may it not be helpful to arrange the papers on the program in groups in some such way as that adopted this year; an individual member could then attend particular sessions, or all sessions, according as his interest and activities are specialized, or more general. A glance at this year's program shows the broad scope of the combined interests of the members of this Association; and this scope is sure to become still broader as internal medicine grows and specialization in its various subdivisions increases. Thus, before long, the problems of "social medicine" are likely to engage us more than they do now. And I should like, in closing, to refer for a moment to this topic. Society at present tries, for its own welfare, to educate all citizens of the State. It may soon decide to try also to maintain the health and efficiency of all. Should society so resolve, a great extension of the municipal, State, and Federal medical services would become necessary to prevent disease; and the present method of treating patients at their homes would, in all probability, be largely replaced by hospital treatment. And if health should come to mean more than mere existence without outspoken physical disease—to include an abundant vitality, the capacity for joyous activity and for successful adaptation to the environment—then society, to maintain the health of its members, would have to see to it that the children born inherit bodies capable of normal responses to environmental stimuli, and further, that the various environmental stimuli to which individuals are exposed are beneficial to them and not too injurious. Such an ideal campaign for health seems at present a mere dream. But some dreams are prophetic forerunners of reality, and if we are to judge of the future by certain

signs in the present, say by the institution of the *Krankenkasse* in Germany and by the movement toward a national medical service as advocated by Lloyd George in England, it may not be long before we shall, in this country, too, be taking some important steps forward in "social medicine." And when the time for this is at hand, we can be sure that this Association of American Physicians will be ready to throw its influence in the direction most helpful to society as a whole.

STUDIES ON THE NATURE OF BIOLOGICAL SPECIFICITY

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(From the Hearst Laboratory of Pathology and Bacteriology, University of California)

In studies in collaboration with T. Brailsford Roberston, extending over a period of nearly three years, attempts have been made to gain some insight as to the nature of biological specificity. For this purpose the antigenic properties of derivatives and compounds of the purest obtainable protein, namely, casein, have been studied.

In a general way, the antigenic properties of each substance were tested by their ability to produce precipitins or fixation antibodies in rabbits, and second, by their ability to sensitize guinea-pigs for subsequent anaphylactic intoxication by the same and other substances. As the relative percentages of the amino-acids occurring in a given protein is one of the most characteristic properties of such a protein, attempts at first were made to immunize or to sensitize animals with combinations of the two amino-acids that are present in largest amounts in casein, namely, glutamic acid and leucin. As had been found by other observers in the case of a single amino-acid, such combinations of amino-acids were likewise non-antigenic. Casein, in the course of its peptic hydrolysis, produces first a substance designated paranuclein. The antigenic properties of this substance and of the complete peptic digestion of casein were tested. Paranuclein was found to be antigenic, but the complete peptic digestion product was non-antigenic. Animals sensitized either to casein or to paranuclein react indistinguishably with either substance. Both substances produce antisera which are, to a certain extent, quantitatively specific.

These experiments failed to prove the residence of specificity in any distinguishable fraction of the protein. Attempts were then made to determine the genesis of specificity in the protein built up from one of its derivatives. Such a substance has been described by Robertson as the result of the synthetic or reversible action of pepsin, either at 36° or at 60°. The action of pepsin on the products of peptic hydrolysis of casein gave rise to a substance that by chemical analysis was indistinguishable from paranuclein. A test of the antigenic properties of this synthetic paranuclein proved that it was indistinguishable from a paranuclein hydrolyzed from casein. Inasmuch as the products of peptic hydrolysis are non-antigenic, the action of pepsin had produced an antigenic property in producing this synthetic paranuclein.

The latter part of the work has concerned itself with the antigenic properties of compounds of the antigenic protein (casein) with a non-antigenic protein. Two such products have been studied. Kossel has pointed out that when members of the protamin group are mixed with other proteins in weakly alkaline solutions, precipitates are produced. These compounds he regards as analogous to the naturally occurring histons. The first of these which we produced, protamin or salmin caseinate, the salmin having been derived from salmon eggs, failed to give any conclusive results in its immunological relations. An antiserum to protamin caseinate reacted with casein and with protamin caseinate owing to the presence of the casein in the latter compound. Far more significant results, however, were obtained in the experiments with another compound, namely, casein compounded with globin. Although the anaphylaxis experiments with this compound were unconvincing, it was found that an antiserum to globin caseinate gave the fixation reaction not only with globin caseinate and casein, but also with globin, which latter substance does not in itself produce an antibody. In other words, the modification in globin brought about by its compounding with casein has produced antigenic or specific properties.

These studies emphasize the need of further investigation with similar compounded proteins.

DISCUSSION

Dr. V. C. Vaughan: The results of Dr. Gay's work are confirmatory of what has been held by some of us for years: that there is present in the protein molecule a specific antigenic body. Zundt has been working on this subject and has found a proteose which has the property of sensitizing animals without being itself poisonous; the work here presented by Dr. Gay is thus in the same direction.

THE FUNCTIONS OF THE DIAPHRAGM AND THEIR DIAGNOSTIC SIGNIFICANCE

By C. F. HOOVER, M.D.
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A CLEAR understanding of the respiratory role of the diaphragm is necessary to analyze respiratory movements in the thorax and abdomen.

In former years the inspiratory excursion of the diaphragm was grossly exaggerated by estimating the excursion of the lower borders of the lungs and the liver as a measure of phrenic movement.

These were misleading because the descent of the lung in the pleural sinus to an extent of 6 cm. may be accomplished by the diaphragm descending or withdrawing from the thoracic wall only a distance of 1 cm.

The inspiratory descent of the anterior hepatic border is an exaggeration of phrenic movement because the liver rotates on a transverse axis and is not depressed *in toto* during inspiration. This axis of rotation is marked by the posterior hepatic border or that liver portion which is not covered by peritoneum. This part of the liver is fixed by reflections of the peritoneum from the liver to the under surface of the diaphragm and posterior abdominal wall.

Inspiratory movements of the diaphragm, therefore, rotate the liver forward and downward. The rotating force is applied on the posterior and superior portion of the upper surface of the liver and therefore the excursion of the anterior border of the liver corresponds to the excursion of the weight end of a lever of the third class, the fulcrum being at the posterior hepatic border and the power is applied at the posterior portion of the upper surface of the liver. So the descent of the lower pulmonary and anterior hepatic borders are gross exaggerations of phrenic excursion.

In recent times the fluoroscope has given us more accurate con-

ceptions of the inspiratory descent of the diaphragm. A very good example of this magnification of phrenic descent is seen in pericarditis with effusion. Several years ago a patient with purulent pericarditis of pneumococcus origin came under my observation. The liver in this instance presented a great rounded tumor on the right side of the abdomen with its anterior border rotated downward in the iliac fossa. Paracentesis of the pericardial sac was performed, and although only 700 c.c. of pus were removed, when the aspiration was finished, the anterior border or edge of the liver occupied its normal position at the right costal border.

All discussions of the function of the diaphragm which have appeared in recent years contain recognition of two movements at the base of the thorax which are caused by diaphagmatic contractions: (1) Retraction of the hypochondria, and (2) widening of the subcostal angle or divergence of the costal borders.

Keith[1] in his article on Respiration in Man refers to Duchenne's experiments and deductions which amounted to proving that diaphragmatic action contributed to widening of the subcostal angle and spreading of the hypochondria by virtue of the piston action of the liver, spleen, and stomach which are driven downward and forward thus spreading the upper lateral abdominal boundaries. All modern works on physiology and anatomy refer to Duchenne's experiments and unite in maintaining the validity of his deductions.

When one attempts routinely to analyze the respiratory excursion of the thoracic walls in a service of patients with varied thoracic and abdominal conformations and with varied thoracic and abdominal diseases it will be found that Duchenne's explanation is not tenable.

1. It is proposed to show in the following discussion that the resultant of phrenic contraction always tends to narrowing of the subcostal angle, retraction of the lower end of the sternum, and retraction of the internal portions of the hypochondria above the level of the ninth costal cartilages.

2. Although the action of the diaphragm is correlated with the action of the scaleni and intercostal muscles, the diaphragm is the

[1] Further Advances in Physiology, 1909, p. 182.

antagonist of the other muscles in their efforts to enlarge the transverse and anteroposterior diameters of the base of the thorax and also acts as an antagonist to the tendency of these muscles in their inspiratory activity to lessen the longitudinal diameter of the thorax and lengthen the longitudinal diameter of the abdomen.

3. There is twofold purpose in the contraction of the diaphragm, viz., to maintain the integrity of the longitudinal diameter of the thorax against the inspiratory effect of the scaleni and intercostals and also to enlarge the longitudinal diameter of the thorax.

4. The resulting variations in respiratory movements of the lower end of the sternum, subcostal angle and costal borders from the ninth rib to the subcostal angle, the epigastrium and hypochondria all depend on the higher or lower positions of the diaphragm.

5. When the diaphragm is pushed upward it is placed at a mechanical disadvantage in approximating the points of origin and insertion of its muscle, viz., the central tendon, sternum, and costal borders. But when the diaphragm is displaced downward the muscle is placed at a mechanical advantage for its affect on the movement of these structures.

6. However high or low the diaphragm may be placed, so long as its muscle is active the longitudinal diameter of the thorax is either maintained or enlarged by its action.

Although all these propositions seem very simple and are easily explained, the want of a satisfactory understanding of the function of the diaphragm has made it impossible to make a critical analysis of respiratory movements of the thorax in any and all diseases.

The so-called Litten diaphragm phenomenon is of service in estimating the excursion of the lower border of the lungs, but it is such a small part of the many evidences of respiratory movement at the lower thoracic aperture, that when it is absent the phenomenon is not of any diagnostic service. Several monographs on diaphragmatic function have been published from German sources,[1] but they deal only with the effect of phrenic contraction on the

[1] Spiel des Zwerchfells, E. Zabele, Berlin, 1906; also Allgemeins d. Spezielle path. Zwerchfells. By H. Eppinger, Wien, 1911.

pleural sinus. The more important manifestations of diaphragmatic activity are disregarded because the antagonistic relations between the diaphragm and scaleni have not been taken into account.

In the dog in health and disease the diaphragm and its antagonists produce respiratory movements of the lower end of the sternum, subcostal angle, costal borders, epigastrium, and hypochondria, identical with those seen in human beings. In man, spasm of the diaphragm causes retraction of the lower end of the sternum, narrowing of the subcostal angle and violent approximation of the hypochondria toward the median line. When this function is seen in diaphragmatic pleurisy or mediastinitis in man we are in doubt about the movements resulting from diaphragmatic action alone. The transverse abdominal muscles may also contribute to the movements. If the linea alba of the dog is slit from the sternum to the pubes and the abdominal walls on both sides are cut transversely to the quadratus lumborum then muscular activity of the abdominal walls can be eliminated as a factor in movements of the costal borders.

After these preparatory incisions, electrodes are placed on the right and left leaflets of the diaphragm. When the diaphragm is then stimulated by a strong electric current the sternum, subcostal angle, costal borders, and hypochondria exhibit the same movements as are seen during phrenic spasm in man. When the three roots of the phrenic nerve of the dog are cut on both sides so the diaphragm is completely paralyzed, then the inspiratory widening of the subcostal angle and flaring of the hypochondria during inspiration are much exaggerated over the same movements which occur when the phrenic nerves are intact.

A few months ago we had a child at Lakeside Hospital whose arms and legs and diaphragm were completely paralyzed from poliomyelitis. The scaleni and intercostal muscles were intact. The respiratory movements were identical with those of the dog whose phrenic nerves were severed.

The subcostal angle showed an exaggerated widening during inspiration. The costal borders and hypochondria diverged from the median line, and the epigastrium was retracted during inspiration. In other words, the scaleni and intercostals had no antagonist

to modify their inspiratory movements of the hypochondria and costal borders.

A man, aged forty-seven years, was operated at Lakeside Hospital six months before his second admission to the hospital on account of empyema of the gall-bladder, drainage was established, and in about two months the drainage from the gall-bladder ceased, the sinus closed and the patient was perfectly comfortable during a period of four months when suddenly he was seized with chills and fever and severe pain in the right hypochondrium and over the right deltoid muscle. A week later he was admitted to the medical wards and presented all the characteristic physical signs of a large amount of fluid in the right pleural cavity. The right thorax was larger than the left. The right side was flat on percussion from the clavicle to the edge of the liver which was located two inches below the costal border in the nipple line. The physical signs on auscultation and percussion were characteristic of a pleural cavity filled with fluid. The one sign which was at variance with thoracic empyema was the fact that the affected side had a larger excursion and particularly the right costal border diverged much more from the median line than did the left costal border. This fact indicated a loss of function of the diaphragm and suggested an infraphrenic abscess had ruptured through the diaphragm into the right pleural cavity or at least a myositis of the diaphragm had resulted in a loss of its muscular function. For had the diaphragm been displaced downward by the empyema and had the phrenic musculature been left intact, then the activation of the phrenic muscle would have fixed the right costal border so as to prevent its divergence from the median line or the right costal border would have been drawn toward the median line during inspiration. Evidently the scaleni and intercostal muscles of the right side were not opposed by the normal antagonistic action of the diaphragm. Unfortunately, the patient's critical condition at the time of operation did not admit of definitely determining whether there was or was not an opening through the diaphragm. Two weeks after the empyema was drained the patient's costal borders moved symmetrically during inspiration.

Another patient developed signs suggesting thoracic empyema

following appendicitis. The base of the right thorax was dull, tactile fremitus was diminished, auscultation revealed a diminution of the intensity of the respiratory sounds attended with elevation in pitch of the inspiratory and expiratory sounds.

All these physical signs were strongly suggestive of thoracic empyema. But one sign alone gave the key to the diagnosis. The costal border of the affected side had a greater lateral excursion than the sound side. This fact could have only one interpretation and that was a loss of the normal antagonism of the diaphragm to the action of the scaleni and intercostals of the affected side.

In conjunction with the other physical signs mentioned, this sign indicated an upward displacement of the diaphragm and led to the diagnosis of a subphrenic abscess.

An operation was performed to establish drainage and the entire accumulation of pus was found beneath the diaphragm.[1]

Upward displacement of the diaphragm diminishes the inspiratory restraint of the costal borders, because the more its muscle is curved the less will be the resulting traction on its sternocostal attachments. Conversely, the flatter the diaphragm the greater will be the resulting traction on the sternocostal attachments of the diaphragm.

When hepatic enlargements displace the diaphragm in an upward direction then the right costal border will exceed the left costal border in its inspiratory divergence from the median line. Patients with acute jaundice who have swollen livers show this disparity in movement. After the jaundice has subsided and the diaphragm resumes the original position then the two costal borders are seen to have a symmetrical excursion.

When the liver is enlarged in an upward direction sufficiently to displace the lower border of the lung a distance of one intercostal space, this increase in the excursion of the costal border is distinctly visible. Paresis of the diaphragm or accentuation of the convexity of the diaphragm will serve to increase the inspiratory divergence of the costal border from the median line. An upward displacement of the diaphragm will not serve to increase the movement of the costal border on the affected side if the displacement

[1] This observation was made by Dr. H. L. Taylor, Resident Physician at Lakeside Hospital.

is caused by an obsolete pleurisy with synechia between the diaphragm and the thoracic wall.

This is particularly true when the site of the synechia is in the anterior portion of the pleural sinus.

A patient who recovered from bilateral pleurisy had the usual characteristic signs of obsolete pleurisy, viz., dulness, diminished excursion, diminished tactile fremitus and lessened intensity of the respiratory murmur without elevation in pitch of the respiratory sounds or any adventitious sounds.

The right costal margin moved away from the median line during inspiration, but the left costal border moved toward the median line during inspiration.

The physician who attended the patient during his illness said the most persistent and most intense dulness and resistance was over the left inframammary region where the most marked signs of thickened pleura and synechia persisted.

This evidence of increased diaphragmatic retraction of the costal border suggested the diaphragm had acquired a mechanical advantage in its traction on the costal border because there was fixation of the diaphragm to the thoracic wall above the costal border, thus giving approximately a straight line to the phrenic muscular strands from the central tendon to the left sternocostal region.

This view was confirmed by the following very simple experiments:

The abdomen of a dog was opened and to avoid the possibility of admitting air to the pleural cavity a thin strip of wood was placed against the under right side of the diaphragm so that the diaphragm over the site of the pleural sinus from the right sternal border to the anterior axillary line was applied to the thoracic wall by a clamp which was applied to the outer side of the thorax and the inner surface of the strip of wood. This gave a high insertion of the diaphragm and resulted in fixation and retraction of the right costal border during inspiration. The same effect on the inspiratory excursion of the costal border was procured by fixing the diaphragm to the ribs about two inches above the costal margin, by means of silk ligatures which were passed through the diaphragm and

thoracic wall with very thin needles. When the ligatures were released, the costal border resumed its original inspiratory divergence from the median line.

This manner of upward displacement of the diaphragm converts the line of traction from a curved to a straight line, thus placing the diaphragm at a mechanical advantage, whereas an upward displacement of the diaphragm which accentuates the curve of the line of traction (as occurs in hepatic enlargement) will place the diaphragm at a mechanical disadvantage. The movements of the costal borders and lower end of the sternum are much more readily affected, of course, by varying elevations and depression of the anterolateral strands of the diaphragm than the changes in the elevation of the posterior strands of the diaphragm. This is apparent from clinical experiences and also from trials made in the experiment on the dog which I have just described. When the posterior portion of the diaphragm was fixed to the thoracic wall over the site of the pleural sinus, the inspiratory widening of the subcostal angle was not modified. Thus far the discussion has dealt with clinical and experimental evidences which show the subcostal angle is enlarged during inspiration by the action of the scaleni and intercostal muscles and also that impairment of the diaphragmatic muscle or paresis from disease or cutting the phrenic nerves or accentuation of the arch of the diaphragm will contribute to the inspiratory widening of the subcostal angle.

We can now see the errors involved in the interpretation of Duchenne's experiment of driving the diaphragm upward by bandaging the abdomen of the dog and thus increasing the longitudinal diameter of the abdomen at the expense of the longitudinal diameter of the thorax. The accepted interpretation of this experiment is, the diaphragm thus being prevented from encroaching on the longitudinal diameter of the abdomen by its contraction, expends its force in elevating the costal borders and widening the subcostal angle.

The correct interpretation of Duchenne's experiment lies in the fact that an increase of the convexity of the diaphragm without altering its insertion in the anterolateral thoracic wall places the diaphragm at a mechanical disadvantage and thus contributes

to widening of the subcostal angle by the action of the scaleni and the intercostal muscles.

Downward displacement of the diaphragm will place the diaphragm at a mechanical advantage in restraining the divergence of the costal borders and thus causes a diminution of the inspiratory widening of the subcostal angle, and may cause retraction of the lower end of the sternum, narrowing of the subcostal angle, and approximation of the anterior hypochondria toward the median line.

My attention was first called to these phenomena in pulmonary emphysema. A moderate degree of pulmonary emphysema will cause the pleural sinuses to be filled with the enlarged pulmonary borders and still the emphysema will not be severe enough to cause cyanosis or an increase of the CO_2 content of the alveolar air above 5.3 per cent. Under these conditions there will still be a distinct widening of the subcostal angle during inspiration. If the degree of emphysema increases, of course the lower borders of the lung can descend no farther than the bottom of the pleural sinus, but this further flattening of the diaphragm causes the subcostal angle to be narrowed during inspiration and the anterior hypochondria will be approximated toward the median line during inspiration. When emphysema is sufficiently severe to cause cyanosis, so the alveolar air will contain 6.5 or more of CO_2, then the subcostal angle will remain the same or it will be diminished during inspiration.

Variations of degree in pulmonary emphysema offer very good opportunities to see just when the critical point in flattening of the diaphragm is obtained.

The first step in emphysema reveals the pleural sinus filled with lung, then as the flattening of the diaphragm progresses the critical point is attained when the subcostal angle remains constant during inspiration and further descent of the diaphragm is attended with inspiratory narrowing of the subcostal angle and inspiratory approximation of the hypochondria. The last condition is always seen when the alveolar air obtains a percentage of CO_2 as high as 7.5 per cent. or more.

When pulmonary emphysema is attended with cyanosis and these

changes in the respiratory movement of the subcostal angle and hypochondria are not apparent then it can be said with certainty the cyanosis is not due to impairment of lung ventilation from emphysema alone, but the cyanosis must then have a contributory cause in some other factor which impairs either internal respiration or the respiratory function of the lung which is quite distinct from the emphysematous disturbance of ventilatory function. Conversely when an emphysematous patient has marked inspiratory narrowing of the subcostal angle and cyanosis is absent, then some other factor besides enlargement of the lung must contribute to the flattening of the diaphragm. Enlargement of the pericardial sack causes inspiratory narrowing of the subcostal angle.

A small pericardial effusion may be demonstrated by other physical signs when the phrenic displacement is so slight that it allows inspiratory widening of the subcostal angle. As the effusion increases the critical point is reached when the subcostal angle remains constant during all respiratory phases and the epigastrium is still protruded during inspiration; when accumulation of fluid in the pericardial sac progresses there will be inspiratory narrowing of the subcostal angle and inspiratory retraction of the epigastrium.

It is this stage of diaphragmatic depression which has often been interpreted as phrenic palsy in pericarditis. The diaphragm is not paralyzed, but is activated during inspiration, and because of its downward displacement, retracts the hypochondria and narrows the subcostal angle. Owing to the flattening of the diaphragm its activation does not cause a further lengthening of the thorax, but the longitudinal diameter of the thorax is maintained and the epigastrium is retracted because the thoracic cage *in toto* is elevated. This elevation of the thoracic cage enlarges the capacity of the hypochondria, consequently the epigastrium is retracted.

Within a day's time the pericardial effusion may be absorbed sufficiently to cause a return to the normal type of respiratory movement of the subcostal angle and the epigastrium. This lack of respiratory excursion of the diaphragm attended with inspiratory retraction of the epigastrium has been incorrectly described as paralysis of the diaphragm in pericarditis.

There can be no paralysis of the diaphragm when the subcostal angle is narrowed during inspiration.

Paralysis of the diaphragm contributes to the inspiratory widening of the subcostal angle. We have had ample opportunity to confirm (at Lakeside Hospital) the effect of pericardial effusion on the inspiratory movement of the subcostal angle and costal borders. A patient with pericarditis who was frequently tapped always exhibited the phenomena above described before and after each paracentesis.

These phenomena are specifically described because one finds in all neurological works very unsatisfactory discussions of the symptoms of paralysis of the diaphragm. And where specific statements are made, as in *La Pratique Neurologique* by Guillain,[1] we find the symptoms of phrenic paralysis are described as showing "inspiratory retraction of the hypochondria and expiratory expansion of the hypochondria, which is the opposite of what is normally seen." This error has evidently arisen from mistaking the evidences of a flattened diaphragm for evidences of diaphragmatic palsy.

Cardiac enlargement may alter the respiratory excursion of either the left or both costal margins. If the enlargement is to the left of the median line only the left margin is affected, if the enlargement is to the median line as occurs in mitral stenosis, then the subcostal angle will be symmetrically narrowed during inspiration.

Thus far only those conditions which cause a widespread flattening of the diaphragm (as in emphysema) or those which cause purely a local flattening of the sternocostal fibers of the diaphragm have been described.

Filling of the pleural sinus laterally and posteriorly will also modify the inspiratory excursion of the costal border on the affected side. This effect is of great service in recognizing pleurisy with effusion and pneumothorax, as both conditions will result in fixation of the costal border or an inspiratory traction of the costal border toward the median line.

[1] P. Marie, 1911, p. 650.

For example, a girl, aged eighteen years, had a pleurisy with effusion on the right side which was unattended with pain. The fluid occupied only the posterior aspect of the pleural cavity. During inspiration the left costal border diverged from the median line. The right costal border was drawn toward the median line during inspiration; 270 c.c. of fluid were aspirated and then the right costal border diverged from the median line during inspiration.

Pleuritic pain accompanying an inspiratory movement will inhibit the excursion of the costal margin during inspiration, but this is quite different from restraint of the costal border in pleurisy with effusion. When pleuritic pain is a factor, the scaleni and intercostal muscles of the affected side are inhibited in their action, so of course the costal border will move very little, but the costal border is not drawn toward the median line. The important point to bear in mind is to determine the movement of the costal border when the actions of the scaleni and intercostals are not inhibited.

This movement of the costal border is frequently of great service in differentiating between pulmonary infiltration of the lower lobe of a lung and pleurisy with effusion, and also in differentiating between an obsolete pleurisy and pleurisy with effusion when the obsolete pleurisy does not involve the sternocostal portion of the diaphragm.

Consolidation of the lower lobe of the lung and obsolete pleurisy may diminish the excursion of the costal margin, but there will be some movement, and that will be away from the median line and not toward it as occurs in pleurisy with effusion.

Pneumothorax causes inspiratory traction of the costal border toward the median line on the affected side as can be readily seen in man and produced in dogs by the admission of air to a pleural cavity. Air was admitted to the right pleural cavity of a dog and directly the costal margin of the right side was seen to move toward the median line during inspiration.

All the roots of the right phrenic nerve were then cut and directly the right costal border diverged from the median line during inspiration, although the diaphragm occupied a very low position. The diaphragmatic attachments to the right costal border were then

cut and the lateral excursion of the right costal border during inspiration was greatly increased.

Keith[1] says, "The writer, from observations made by the *x*-rays, has come to regard a free movement of the subcostal angle as an index of a free action of the diaphragm." This statement is literally true but not in the sense in which Keith interprets the phenomenon. If the diaphragm is activated in a normally arched position or in a position higher than normal there will be a marked excursion of the diaphragm and inspiratory widening of the subcostal angle. In this sense activation and excursion of the diaphragm are attended with widening of the subcostal angle, but the inspiratory widening of the subcostal angle is not due to activation of the diaphragm but to activation of the muscles which lift the thoracic cage. When the convexity of the diaphragm is flattened its activation will be quite as strong as when the diaphragm has a maximum convexity, but phrenic activation in a lowered position manifests itself in fixation or narrowing of the subcostal angle.

Briefly stated: Movements of the costal borders during respiration give valuable aid in differentiating between supraphrenic and subphrenic disease.

Also in differentiating between pulmonary consolidation and pleurisy with effusion, and in differentiating between obsolete pleurisy and pleuritic effusion.

Costal border movements enable us to form a comparative estimate of a degree of pulmonary emphysema which exceeds mere filling of the pleural sinus with aërated lung. Movements of the costal borders give indication of the amount of fluid in a pericardial sac and also contribute to an appreciation of cardiac enlargement and an appreciation of the relative enlargements of the two ventricles. Unlike the diaphragm phenomenon of the pleural sinus, these movements of the costal borders and the subcostal angle are always present and can be accurately observed whatever the disease may be and however thick may be the panniculus adiposus. So the usefulness of these signs has a much broader

[1] Respiration in Man. Further Advance in Physiology, Leonard Hill, p. 199.

and more accurate diagnostic significance than the so-called Litten diaphragm phenomenon.

In conclusion, a word of caution should be added. In making an estimate as to whether a costal border is stationary or diverges from, or is drawn toward the median line, the examiner should apply his thumbs symmetrically placed along the costal borders to serve as indicators. Inspection alone without the aid of palpation of the borders may lead to confusion between elevation of the thoracic cage and widening of the subcostal angle. The thoracic cage may be strongly elevated and still the subcostal angle remain the same size. In fat persons, asymmetrical movements of the costal border may be obscured without the aid of indicatory palpation.

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DISCUSSION

Dr. Lewis A. Conner: I understood Dr. Hoover to say that any cause that increases the convexity of the diaphragm will place it at a mechanical disadvantage. I would reach just an opposite conclusion, for with descent of the diaphragm, the fibers of that muscular dome more and more merely pull in opposed action. I would like Dr. Hoover to explain this statement more clearly.

Dr. Hoover: The diaphragm has two functions to perform: (*a*) To maintain the integrity of the longitudinal thoracic diameter, and (*b*) to increase (by descent) the longitudinal thoracic diameter. In a low position, the diaphragm, instead of merely maintaining the integrity of the longitudinal thoracic diameter which tends to be shortened by the lift of the scaleni and intercostales, is at a mechanical advantage and its traction causes a narrowing of the subcostal angle and an inward movement of the costal borders.

THE ACTION OF INTRAVENOUS INJECTIONS OF VARIOUS SUBSTANCES IN ANIMAL AND HUMAN CANCER

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Through the extension of our knowledge of those substances which act upon carcinoma in animals, we hope to obtain the data necessary for the understanding of the mechanism through which those substances exert their influence, and we also wish to determine whether those substances which act on mouse carcinoma also act on human cancer. At the present stage of our investigations it seems to us of very much greater importance to determine whether or not those substances active in the case of animal cancer are also active if only slightly so in the case of human cancer, than to find a substance able to cause a complete cure of cancer. The aim of our investigations at the present time is principally a theoretical one.

We considered so far two classes of substances in regard to their action on mouse carcinoma: (1) Colloidal metals as well as a colloidal preparation of sulphur. All these substances were prepared according to Bredig's method. and we compared their action with the effect of ionized inorganic salts; (2) solutions of various albuminous substances, as well as solutions of carbohydrates and lipoids. Furthermore, we tested hirudin, which has a strong

inhibiting effect on the coagulation of the blood. We used in the main two criteria for the action of the various substances on the tumor. We examined the influence of one single intravenous injection of a certain substance on a tumor, the examination being made twenty-four hours after the injection. Secondly, we made a series of four or five and sometimes more injections, one injection being given every twenty-four hours and observed the influence of these injections on the rate of growth of the tumors during the time of the injections and in the period following the injections. We may summarize our results as follows:

Of 46 tumor mice injected with solutions of colloidal copper, 35 did not grow during the period of injections and 11 grew, but definitely less than controls. Colloidal platinum has approximately the same effect as colloidal copper. Recently, Izar stated that one injection of collodial sulphur caused in many cases a complete necrosis of the tumor. Our solutions of colloidal sulphur, which contained a considerable amount of platinum, showed some effect, which, however, could easily be explained by the presence of the platinum in the solution. In other experiments in which the amount of sulphur in the solution used was greater, and which, on account of the thrombosis in the veins caused by the injection, could only be injected twice in each mouse, no effect was noticeable on the tumors. We could therefore not notice any pronounced efficacy of the colloidal sulphur which we used. We also tested various preparations consisting of combinations of copper and casein. Some of these preparations had a similar retarding effect on the tumor growth as the colloidal copper. We also used a preparation of copper in combination with an albuminous substance unknown to us, manufactured by von Heyden. One single injection of this substance caused, in the majority of cases, considerable softening and necrosis in the centre of the tumor. Repeated injections inhibited, in the large majority of cases, the growth during the time of injection. In order to test whether the condition in which the copper was introduced in these experiments was responsible for the positive results obtained, we made some experiments in which we injected solutions of copper nitrate intravenously into mice. We found that during the period of injections the tumor

continued to grow. This substance is therefore ineffective. To a few mice we gave injections of mercury bichloride. This substance also was ineffective—we must state, however, that on account of the changes in the bloodvessels produced by the latter substance, the number of injections given had to be limited. We also tried another inorganic non-colloidal substance, namely, a salt of lanthanum. This also was without effect on tumor growth. We may therefore conclude that the colloidal condition in which the metal is introduced is of great importance in the results obtained. We injected a few mice with ethylhydrocuprein, a preparation which had been found very effective in cases of pneumococcus infection in animals in the hands of Morgenroth. This substance was without effect on tumor growth.

Passing now to the more complex organic colloidal substances, we may briefly summarize our result as follows: Various casein solutions procured through chemical factories, as well as casein purified in our laboratory, inhibited the growth of the tumors during the period of injections in a majority of cases. One single injection of these substances caused, in the majority of cases, a very marked softening and necrosis of the central parts of the tumors. Various preparations of casein which were obtained through interaction between H_2S or flowers of sulphur and casein acted in a similar way. One or several injections of nucleoproteid prepared either from lymph glands or from kidney acted in a similar manner as casein, but this substance was perhaps not quite so effective. To give some figures we may state that after injection of casein or casein sulphur preparations, one single injection caused a very marked softening and necrosis of the central parts of the tumor in 112 tumor mice, while in 21 tumor mice a partial softening and necrosis took place in the centre. The effect was only slight in 43 cases and absent in 25 tumor mice. Repeated injections of casein caused a complete inhibition of growth during the period of injections in 72 cases, while in 30 cases the tumor grew less than the controls, and in 4 cases it grew as well as in the controls. While the efficiency of these substances is unquestionable we find on the other hand that the large majority of other albuminous substances and also a carbohydrate and lipoid were without effect or that the

effect was so slight that it could not be definitely established. The following were such inactive substances tested by us: serum globulin, horse serum, egg-albumen, gelatin, Witte's peptone, protamin prepared according to Kossel's method, starch, and lecithin. We also tested tuberculin and found it quite ineffective. With all those substances there was no central necrosis and softening after a single injection, nor was there any inhibition of growth during a period of several injections. We found, however, one more substance effective and possibly more effective than any of the other substances used in our previous experiments, namely, hirudin. Hirudin not only causes in almost all cases an inhibition of growth during the period of injection, but in a number of cases it also seemed to cause a retrogression of the tumor, a fact which we have not been able to observe with any of the other substances used by us so far. After one injection very marked softening and necrosis of the greater part of the tumor were noticeable. A combination of nucleoproteid and hirudin had approximately the same effect.

In those cases in which, during the period of injections of the various substances, an inhibition of growth was observed, the tumor resumed its growth very soon after cessation of the injections. In some cases a latent period of six to eight and sometimes more days intervened between the last injection and the resumption of the growth. In cases in which, after the injection of hirudin, a retrogression of the tumor had taken place, the retrogression continued in a number of cases after the cessation of the injections. After the injection of hirudin, the retrogression of tumors was, in a number of cases, so pronounced that we think it very improbable that in those cases we had to deal with a spontaneous retrogression. We intend, however, to test still further this question in future experiments. In all cases in which we introduced the substances through other channels than the veins we obtained negative results. In some experiments we determined the smallest amount of casein which was still active and found 0.05 c.c. of a $1\frac{2}{3}$ per cent. solution given in a single injection was effective, while 0.01 c.c. of the same solution was found to be without effect. While in our ordinary routine experiments we gave usually 4 or 5 injections of the substances on successive days, in a few experiments we

injected either a full dose or one-half of the usual dose of colloidal copper on ten successive days. Even in these cases we did not find a cumulative effect of the colloidal copper and no retrogression of the tumors could be obtained after an injection of one-half of the ordinary dose on ten successive days. We even found that the majority of tumors began to resume their growth under this condition. In all these experiments the age of the tumor is of some importance in determining the results of the injections. We found that when we used very young tumors, two or three days after inoculation, or even slightly older tumors, injections of colloidal copper on four or five successive days were unable to check the growth of the tumors, while tumors nine to twelve days old were easily inhibited in their growth.

If we examine, microscopically, tumors which had been under the influence of injections of either casein, nucleoproteid, or colloidal copper, we find that the peripheral areas which were usually preserved, showed more or less numerous mitoses in the tumor cells. Sometimes we observed in the tumors some hemorrhages, especially after injection of nucleoproteid, but otherwise the microscopic studies did not contribute much to the clearing up of the mechanisms of the action of these substances.

In order to get a further insight into the mode of action of these substances, we tested their effect under some other conditions. Dr. W. E. Leighton tested the action of colloidal copper, casein, and nucleoproteid on wound healing in the mouse; he found that notwithstanding the injection of these substances the wound healing follows approximately a normal course. We are, however, investigating still further, at the present time, whether or not some histological alterations are produced under the influence of these substances. We also tested the action of daily repeated intravenous injections of colloidal copper and of one single intravenous injection of casein and nucleoproteid on experimentally produced placentomas in the guinea-pig and rabbit. We usually found after an injection of casein and nucleoproteid more or less pronounced hemorrhage, and consequently partial necrosis in the placentomas of the guinea-pig. In the preserved part of the placentomas, mitoses were still visible. After injections of copper solutions some

superficial hemorrhages and necrosis were occasionally visible, but on the whole very little if any specific effect was noticeable. In rabbits we observed that even pregnancy could proceed normally during the periods of the injections of colloidal copper.

We furthermore tested the effect of there substances on normal guinea-pigs and rabbits. Here we found, in experiments carried out during last March, after injections of nucleoproteid as well as casein, serum globulin, and perhaps protamin, small, scattered areas of necrosis in the liver of guinea-pigs. We find, microscopically, usually small but sometimes even larger conglomerated necroses characterized by a change in the staining of the cytoplasm and by a shrinking of the nucleus of the liver cells. These necrotic areas are situated approximately midway between the portal and central areas of the acini. Very soon polymorphonuclear leukocytes immigrate into the necrotic areas. So far we have been unable to observe similar necroses either macroscopically or microscopically in the liver of mice treated in the same way.

This is a résumé of the main results which we obtained so far in our study of the action of various substances of animal tumors. We now wish to report briefly on some analogous experiments carried out in the case of human tumors.

Here, naturally, our experiences are very much more limited than in the case of animal tumors. And there is one important difference between our work concerning animal and human cancer. While working with animal cancers we are able to carry out our investigations systematically and to make such a large number of experiments that the principal conclusions can be stated with a great degree of certainty; this does not hold good to the same extent in the case of work on human cancer. Here we have to use cases which frequently vary much in character. Usually we cannot obtain a sufficient number of tumors of the same kind. We are therefore not in a position to obtain the same degree of certainty which we expect to obtain in our laboratory work. At present we cannot govern the variable factors in the case of human cancer. These difficulties become still larger if a pathologist enters into what is to him at least at first a new field, and when he has to depend in the beginning to a great extent on the judgment of others. Still, I

believe that, notwithstanding these difficulties, we can arrive at some conclusions.

In patients we used so far two substances, namely, colloidal copper, and in a number of cases various solutions of casein; in some cases alternating injections of colloidal copper and casein were used. It is impossible here to enter into a detailed consideration of the various cases here treated, but our results were approximately as follows: All cases which are rapidly growing cannot be markedly influenced by this treatment. Possibly a slight retardation of growth can occasionally be obtained for some time at least. Those cases in which there are metastases in internal organs, for instance, the liver or lungs, or which are cachectic, can apparently not be benefited. If, on the other hand, we consider tumors frequently inoperable, such as rodent ulcer, carcinoma of the lip, cheek, infiltrating the deeper tissue down to the mucosa of the mouth, we can, in a certain number of cases, cause a partial retrogression of the tumor. In some cases of rodent ulcer which had been progressing for many years, destroying the eye, a part of the wound of the ulcer became covered by skin under the influence of our treatment. In cases of rather extensive cancer of the lip, we may occasionally see a noticeable reduction in the size of the tumor; and if there has been deep ulceration, we may see some shrinking of the ulcerated area through contraction of the surrounding tissue. The ulcer may, in the most favorable cases, heal almost entirely, but even in those cases the healing has not been quite complete. In one of two cases of cancer of the face at least we can be certain that relatively small cancerous areas were left around the ear. In some cases with multiple lesions healing can be produced in one part of the body; for instance, an ulcer of the hand may greatly improve, while an ulcer of the cheek may only be checked in its progress for a certain period of time. But not only are cancers of the skin affected by these injections, but the examining gynecologist found in a carcinomatous mass filling the abdomen a diminution in size under the influence of injections of colloidal copper. In one case the gynecologist found a marked diminution in the size of cancerous masses left in the pelvis after a complete hysterectomy. In two other

similar cases a reduction in the size of the tumor could not be obtained. Especially in cases in which patients were cachectic at the time of treatment the results are usually not good. In a case of carcinoma of the thyroid, the injections of copper produced some diminution in the size of the tumor and loosening of the surrounding tissue, and caused it to become more sharply demarcated from the surrounding tissue. In a case of carcinoma of the larynx with a rapidly growing metastasis in a lymph gland of the neck, some reduction in the size and softening of the lymph gland, and a slight reduction in the size of the carcinoma of the larynx, were obtained.

Casein injections exert a distinct influence on cancer in some cases if the general reaction which follows the injection is very marked. After a very marked general reaction we found, for instance, some very severe lesions of the face in a case of multiple carcinoma of the skin to heal. In another similar case, after a very marked general reaction, some skin began to grow over a rodent ulcer which had led to the destruction of the eye and which had not been influenced much by colloidal copper. In a case of sarcoma of the humerus in a young girl, a diminution in the size of the tumor, with partial calcification, was obtained, according to the *x*-ray plates. On the whole casein solution did not seem to have as distinct an effect as copper had in some cases. Evidently processes of active immunization take place and soon diminish the action of casein. It seems, however, that through the injections of casein the growth of the tumor can be inhibited in some of those cases in which no reduction in the size of the tumor can be obtained.

We see, therefore, that even in the most favorable cases no cure can be effected at the present time through this mode of treatment, but only a partial retrogression. Almost invariably the effect of the injections diminished the further the treatment proceeded. An increase in dose cannot compensate for the gradual decrease in efficiency.

There is one possible danger connected with the injections of casein. As we stated, we noticed after injections of casein solution small necroses of the liver in the guinea-pig. We had not noticed such necroses in mice injected with this solution, neither have we

found in human beings who have received such injections any changes indicating an affection of the liver. Notwithstanding this, we believe that at the present time we should advise against injections of casein or other protein substances in human beings on account of possible injury to the liver. Another difficulty of the treatment by injections of colloidal metals consists in the fact that the large majority of patients can only be given a limited number of injections of copper solution. The veins become affected and occluded after some time. Furthermore, the effect of the copper is so slow that much patience is required on the part of the patient as well as on the part of the observer. In some cases the general condition of the patient suffers somewhat under the influence of this treatment, but usually after injections of copper solution the general condition of the patient improves, although the number of red corpuscles and hemoglobin may become somewhat reduced. After the injections of the casein there is a distinct leukocytosis noticeable, due to an increase in polymorphonuclear leukocytes. In a number of cases which we examined at a later stage of the injection with copper or casein or after the treatment had been interrupted for a certain period of time, we noticed that the differential count of the leukocytes showed a relative increase of lymphocytes.

We may conclude from our observations that mouse carcinoma and human cancer can be affected in a similar manner and that, comparing the dose given per kilo of animal and man, the copper is not less effective in the case of man than in the case of mice. As to the mode of action of these various substances, we are at present not inclined to assume that they act directly on cancer cells after having been taken into the cell body. We would rather suggest that they act primarily by altering the wall of the capillaries and by increasing their permeability, thus producing transudation and sometimes hemorrhage into the tumor and thus interfering with the nourishment of the cancer cells. Secondarily, they may perhaps act directly on the cancer cells. This is merely an hypothesis at the present time, in favor of which, however, various facts might be cited. It is, however, impossible to go into any further detail on this occasion. Although a partial retrogression of the

tumor is in itself perhaps not of sufficient importance to the patient to encourage this kind of treatment, nevertheless in certain cases it might become, even in its present imperfect stage of practical value, inasmuch as some retrogression in the size of the tumor and a sharper demarcation from the surrounding tissue may considerably facilitate a removal of the tumor by surgical means. How far this mode of treatment in combination with other treatments, such as radium and Röntgen rays, may become of practical value we cannot predict at the present time.

OBSERVATIONS ON THE PASTEURIZATION OF MILK

By W. W. FORD, M.D., and J. C. PRYOR, M.D.
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Nearly twenty years ago it was pointed out by Flügge, then Professor of Hygiene in the University of Breslau, that milk may contain the resistant spores of certain peptonizing bacteria, which develop with great rapidity when the ordinary lactic acid organisms are destroyed by heating to the boiling point, or to a temperature slightly below this. These spore-bearing organisms are endowed with the special property of rapidly peptonizing protein material and because of their inability to produce lactic acid or coagulating ferments fail to clot the milk. They thus may appear in great numbers in boiled milk without manifestly changing its appearance, and may be swallowed by the consumer under the impression that the milk being pasteurized is perfectly safe for drinking purposes. According to Flügge, these organisms may resist the destructive action of gastric juice and passing down to the large intestine there develop in the slightly alkaline contents and give rise to serious derangements of metabolism and even to the acute summer diarrheas of childhood.

Flügge's views have not been entirely accepted particularly in this country where the opinion prevails, in some quarters at least, that his experimental results have not been confirmed by other investigators, and that his observations were too few in number to be broadly applicable. The importance of Flügge's work and the comprehensive character of his experiments in our opinion merit far greater attention than has thus far been accorded them. During the past year, therefore, the attempt has been made to confirm Flügge's observations by an examination of milk from Baltimore and Washington during the course of which seventy-five

samples from the former and fifty samples from the latter city have been studied, including all varieties of dipped milk, bottled milk, pasteurized milk, and certified milk. The results may be summarized as follows: In nearly every instance where milk is heated to a temperature ranging from 65° to 100° C. for periods of time varying from ten to thirty-five minutes and then incubated at 37°, this milk undergoes within twelve to eighteen hours either a rapid violent gaseous decomposition with the evolution of foul odors of proteid disintegration, a coagulation with a subsequent rapid peptonization—a peptonization without coagulation, or rarely a coagulation without peptonization—dependent upon the temperature to which the milk is heated. We have been able to confirm in all particulars Flügge's observations as to the changes which take place in heated milk. Cultures from such samples reveal a great profusion of aërobic spore-bearing organisms, identical with those described by this investigator. In addition to these anaërobes are always present, since heated milk offers most satisfactory conditions for the development of anaërobic bacteria, the aërobic spore-bearing organisms absorbing oxygen at the surface, and the layer of cream preventing the penetration of oxygen to the lower levels. In our experience the most important anaërobe present in milk in this country is *Bacillus aërogenes capsulatus*, or the gas bacillus of Welch and Nuttall, which is chiefly responsible for the violent gaseous decomposition seen especially in samples heated to between 65° and 85° C. There must of course be many other anaërobes present at times, particularly such forms as the classical *Bacillus butyricus* of Hueppe. These changes take place most readily at 37° C., but if milk be maintained at 22° similar changes occur, but with somewhat less rapidity. The organisms isolated from such samples are identical with those found in milk kept in the thermostat. Heated milk kept on ice undergoes as a rule no spontaneous disintegration, but the spores of the organisms present retain their vitality for many weeks and when the specimens are transferred to the thermostat or kept at room temperature, initiate almost the same putrefaction as that already described. Control experiments with raw milk kept under precisely the same conditions reveal only a normal clotting and on cultures only the

ordinary lactic acid bacteria with the occasional presence in rare instances of spore bearers. The gas bacillus is also lacking from such specimens or at least does not reveal itself by the same methods of examination as suffice for its isolation from heated milk.

From these experiments it seems evident that when milk is heated a broad biological law of considerable significance comes into play. Under normal circumstances the great preponderance of lactic acid bacteria in milk inhibits the development of the spore-bearing aërobes and anaërobes, either overgrowing them or preventing their multiplication by means of an excess of lactic acid. Destroy the lactic acid organisms and the way is paved for the excessive development of the other groups. Whether these observations should change current ideas as to the value of the pasteurization of milk or not cannot be stated. In view of the fact that more and more milk is being sold in the larger cities in this country after pasteurization, however, and that the public is being instructed as to the great merits of pasteurization for insuring a supply of milk which cannot convey infection, a note of warning should be uttered. One is confronted with the curious anomaly that the better pasteurization is the worse it is, since heating milk to a temperature surely sufficient to destroy the pathogenic bacteria, which may be present in it will also destroy the lactic acid organisms and convert milk into a substance which is far more apt to undergo putrefactive changes than is raw milk. At all events we feel justified in stating that efficiently pasteurized milk should only be used within a short time after the process is completed and that it is absolutely essential that this milk be kept on ice from the moment of pasteurization until its use. In view also of the fact that methods of pasteurization are in many cities being changed from the flash to the holding process we are inclined to believe that the entire problem of milk pasteurization should be studied more thoroughly from the standpoint of the end-reaction or the final changes which may occur in milk heated to various temperatures.

Finally, there are one or two points clinically which should be emphasized. If anaërobic putrefactive bacteria can develop in the large intestine and by their split products give rise to derangements in health, pasteurized milk can serve as a most prolific

source of such organisms. At the same time these experiments offer considerable experimental evidence to support Metschnikoff's views as to the value of lactic acid therapy. If the lactic acid organisms are able to restrain the development of putrefactive organisms outside of the body they should by analogy be able to perform the same function in the intestinal tract, When derangements of health can be traced to the excessive development of anaërobes in the intestine one would be justified in attempting to overgrow and drive out these organisms by the administration of lactic acid bacteria in great quantity.

DISCUSSION

Dr. W. H. Park: I think if pasteurized milk is used within the ordinary time of consumption under commercial conditions there will be no danger of the remaining spore-bearing organisms over-growing. The changes noted by Dr. Ford are to be seen only two or three days after pasteurization.

Dr. M. J. Rosenau: We have recently obtained results not entirely in accord with Dr. Ford's findings. We have found that when the milk is exposed to 65° to 70° C. for a short time it does sour and coagulate afterward in the normal way. Under such conditions of pasteurization certain groups of lactic acid bacilli survive. Putrefaction changes take place only after the milk has been exposed to high temperatures.

Dr. Ford: We have studied the time in which the putrefactive organisms grow in pasteurized milk; they grow rapidly at 22° C., and they grow when the milk is on ice; and the growth appears during the period of consumption, which in Baltimore may be as long as seventy hours. In the milk samples tested, which has not been high grade milk, we have found no lactic acid organisms surviving exposure to 60° C.

A CLINIC FOR PRECAUTIONARY X-RAY EXAMINATIONS

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AND

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A CLINIC for precautionary *x*-ray examinations has seemed to us for some time desirable, and on November 1, of last year, one was opened in the *x*-ray department by the trustees of the Boston City Hospital, on recommendation of the senior staff, following that of the *x*-ray department. The work is carried on by Dr. S. W. Ellsworth, assisted by Dr. Ralph D. Leonard, and by a trained nurse and a radiographer, under the direction of Dr. Williams. The clinic is for diagnosis only, the patients being referred for treatment to appropriate institutions or to their own physicians. It is held daily, except on Sundays and holidays, in the late afternoon at hours convenient for wage-earners, and when the department is not otherwise much used, thus increasing the usefulness of the plant. The aim of the clinic is to ascertain if certain diseases are present before the graver signs and symptoms have developed, or to indicate that they are probably absent. Naturally time must elapse before the opportunities it offers can be fully realized by the community.

The clinic has also proved of value to patients who are not in the precautionary or anticipatory stage, but are sent by their physicians to obtain the advantage of a method of examination otherwise beyond their means.

The term "*x*-ray examination" as used here denotes an examination that has been carried out:

First, by means of an *x*-ray negative[1] made with a proper length of exposure. The negative is preferable to the print.[2]

Second, by means of a fluorescent screen. In chest diseases, a tube that gives a sufficiently *small* amount of light should be used, otherwise it is impossible to recognize a slight increase in density. In early pulmonary tuberculosis in particular, in order to get the best results it is necessary to have an *x*-ray tube that gives out a little light only, the apparatus so arranged that the light can be turned up or down, and then turned down so low that it will barely go through the normal side of the chest under examination. This method makes any increase in density in the diseased side obvious, when it would otherwise be overlooked, and is most essential. The examination with the fluorescent screen is of value because the organs may be studied in motion, but especially because it enables the practitioner to recognize and, if he so desires, measure an increase in density of the lungs that might not be recognized and cannot be measured by the negative. For instance, some processes in the lungs that might not cause anything more than a congestion of certain areas would be sufficient to cast a shadow that could be recognized by careful use of the fluorescent screen. On the other hand, details that can be seen in the negative are lost on the screen, such as small glands, and increase in density of or about the air passages, calcifications, etc.

Third, the examination by the *x*-ray is always made at this clinic in connection with the usual physical examination.

As examples of the good results that can be obtained by precautionary *x*-ray examinations, let us consider their usefulness in thoracic aneurysms, present or suspected, and pulmonary diseases, especially tuberculosis.

[1] If the negatives are watched during their development it will be seen, particularly in those of the chest, that those portions which the rays penetrate easily develop first, and the order of this development gives some indication of the relative density of the parts.

[2] Prints were shown differing widely from each other, although made from the same negative.

In the first 400 cases examined there were:

FIRST FOUR HUNDRED CASES EXAMINED

1. Aneurysm	6
2. Cardiac	23
3. Special (foreign bodies, pneumonia, fractured rib, etc.)	26
4. Pulmonary tuberculosis	345
	400

PULMONARY TUBERCULOSIS[1]

Clinical Diagnosis		*X-ray Diagnosis*	
Positive	104	Positive	86
		Negative	4
		Suspected	14
Negative	43	Positive	15
		Negative	23
		Suspected	4
		No diagnosis	1
Suspected	198	Positive	87
		Negative	35
		Suspected	44
		No diagnosis	16
		Deferred	16
			345

ANEURYSM. Of the 6 cases of thoracic aneurysm, suspected or found, one patient came to the clinic with the diagnosis of pulmonary tuberculosis, but the examination by the *x*-ray disclosed an aneurysm of the innominate artery. (Fig. 1.) In the 5 suspected cases the *x*-ray showed that only 1 was a case of aneurysm.

CENTRAL PNEUMONIA. Practitioners realize that an increase in density of the lungs, if deep seated, may not be noted by the usual physical examination. This is exemplified not infrequently in patients with so-called central pneumonia, when little or no evidence of the disease is obtained during its earliest period by this method. As the pneumonia extends, however, and, after an interval of some days, comes nearer the surface of the body, physical signs may be observed. On the other hand, the central situation of the disease

[1] The words "positive" and "negative" designate the diagnosis made by the examining physicians on the evidence obtained from the respective methods. In the early stage we are considering most of the patients had of course no sputum.

MAY
1914

FIG. 1.—Patient thought to have pulmonary tuberculosis. *X*-ray examination showed aneurysm of the innominate.

FIG. 2.—J. B., aged nine years, came to the clinic with a diagnosis of bronchitis, but on account of continued cough and malaise his physician desired an *x*-ray examination. This showed a circular shadow in the posterior portion of the right chest, which was considered due to an encysted empyema. Pus was found by inserting a needle, and operation proved the presence of an interlobar empyema.

The circular dark area on the right side is the shadow cast by the interlobar empyema.

is no bar to the effective use of an examination by the *x*-ray, for increased density in a central portion of the lung casts a shadow as surely as one near the surface. In other words, the conditions of both the central and superficial portions of the lungs are accessible. An examination by the *x*-ray in central pneumonia is not "precautionary" in the sense in which the word has been used here, but is a measure of precaution that is worth emphasizing.

Dr. Boehme in the *Medical Record* for March 29, 1913, gives a series of six cases to show the difficulty of making a differential diagnosis between pneumonia and appendicitis. In two of these cases the patients were operated on and the appendix was normal. Dr. Boehme goes on to say that in pneumonia simulating appendicitis the "faulty diagnosis (as proved by operation) gives a mortality of 20 per cent. of the cases wrongly operated upon."

In this connection a statement made in 1901 by one of us[1] is of interest. "It has happened that patients have been operated upon for appendicitis when no inflammation of the appendix existed. The symptoms simulating appendicitis afterward proved to be due to pneumonia. Should there be any uncertainty as to the presence of pneumonia in any such case, the doubt could be set at rest by an *x*-ray examination."

Early Pulmonary Tuberculosis. In early pulmonary tuberculosis an examination by the *x*-ray may show us that there is a slight increase in density in one apex, usually the right, a diminution in the expansion of the affected lung, as evidenced by the shortened excursion of the diaphragm on the diseased side, and the condition of the glands at the hilus of the lung. Thus by means of the *x*-ray: (*a*) earlier information may be obtained than by the usual physical examination, or (*b*) the *x*-ray may render confirmatory or more accurate evidence.[2] It not seldom happens that physicians, although they suspect pulmonary tuberculosis, delay taking serious

[1] The Röntgen Ray in Medicine and Surgery, by Francis H. Williams, M.D., page 192.

[2] A. B. had slight signs of tuberculosis at the apex of one lung, as indicated by both the physical and *x*-ray examinations. Six weeks later the second *x*-ray examination showed that the process had extended uniformly over both lungs, but the second *physical* examination, made at the same time, gave the same results as the first.

action until their suspicions have been confirmed by further development of the disease, as they hesitate to advise a patient, a young adult particularly, to take steps that may imperil his career. If, however, early in the disease additional and confirmatory evidence from another method of examination converts their suspicions into convictions, as we have not infrequently seen, this dangerous delay can be prevented.

Patients who are in an early stage of pulmonary tuberculosis, judged by the usual physical examination, are shown, not rarely, by the *x*-ray to have trouble in both apices instead of one, that is to say, the stage that would ordinarily be called early is a later one than that in which suspicion may be aroused by the *x*-ray. The evidence given by the *x*-ray is especially obvious if one apex only is affected, because in this case the normal side, that is, the clear lung, can be compared with one of increased density.

By early tuberculosis, then, we mean an earlier stage than physicians generally have in mind when they use this term, a stage so early that there is little or no cough, few or no physical signs, before the patient has infected others, and when recovery is probable.

The following three cases are illustrative and show the value of precautionary x-ray examinations:

The first patient (M. R.) was one of a group of wage-earning girls living under the oversight of a devoted woman, who had been told of the clinic, and had thus had her suspicions aroused in regard to one member of the group. This girl was aged twenty years, had an afternoon temperature of 99.8°, but no cough and no hemoptysis. The examination by the *x*-ray gave a characteristic picture of early pulmonary tuberculosis.

It is well known that if one member of a family has had this disease, other cases will often develop. We believe that a careful examination by the *x*-ray of members of such families or closely associated groups of persons will sometimes reveal cases that would otherwise not be recognized. Therefore, following our rule, we endeavored to examine other members of this group, and one of them, aged twenty-two years, who had been more with the tubercular patient than the others came to the clinic. She had an afternoon temperature of 100°, but a careful physical examination

revealed nothing in the lungs, although the chest was one easy to examine. The *x*-ray, however, showed a well-defined increase in density in the right lung, and this condition was confirmed at another *x*-ray examination made about two weeks later. (A second examination is necessary after an interval of a week or two in order to exclude any acute passing condition that might possibly give rise to similar signs). Soon after the second examination was made she had a positive von Pirquet reaction. This young woman probably has an early pulmonary tuberculosis, which would have been overlooked without an *x*-ray examination.

The third case is that of a woman, aged forty years, who had had a slight cough and a little blood-streaked sputum. The blood it was thought came from the nose or throat. Careful physical examination of the chest gave no evidence of pulmonary tuberculosis. By *x*-ray examination, however, there were well-marked signs of tuberculosis in both lungs, and a diagnosis of this disease was made, which was confirmed later by the finding of tubercle bacilli.

The question naturally arises, "How often is it possible to find patients in what we call, as defined above, an early stage?" At present, not as often as could be wished, for patients do not come sufficiently early, many in the very early stage not realizing that anything serious is the matter with them. The desired end will be best attained by the education of the community.

Early diagnosis promotes recovery and is also a protection to the community, especially when it anticipates the stage of expectoration.

The financial value of such clinics is evident when we consider that the life of a young adult has been estimated to be worth to the community $2000, more or less. It would, therefore, require only a few cases to yield a large return above the yearly cost of such a clinic.

It need hardly be said that no method of examination is infallible, but aided by this method we are not infrequently assisted to an earlier or to a more correct diagnosis, or to both.

DISCUSSION

Dr. R. C. Cabot: The establishment of the clinic described by Dr. Williams is an admirable idea. The good it will do will be proportional to the care and reserve with which the term "positive by *x*-ray" is employed. We say that the result of examination of sputum is positive for the tubercle bacillus, and this is admissible, for the finding is positive for one particular thing. We are, of course, grateful to Dr. Williams for this work and for his paper descriptive of it, but I think it important that we should always interpret *x*-ray pictures as shadows and not as lesions.

Dr. Lewis A. Conner: To carry Dr. Cabot's warnings a step farther, I would express the hope that the convenience and valuable possibilities of *x*-ray examination will not tempt clinicians to allow skiagraphy to supplant careful physical examination; this temptation is a real one, but should sedulously be avoided.

Dr. Williams: I am glad of the comments made in discussion, as they draw attention to one of the points of the paper, namely, that a careful physical examination is always made at this clinic in connection with the *x*-ray examination and of course always should be made. Further, it may be suggested that physicians who have used both methods for a large number of patients should be able to interpret better the physical examination than if they had not been in the habit of having this examination checked by that of the *x*-rays. I have always emphasized my belief that *x*-ray examinations were a part only of a complete physical examination, but in some cases a most important part.

The words "positive" and "negative" in the table indicate the diagnosis of the examining physicians made on the evidence furnished by the usual physical examination and the *x*-ray examination respectively. The patients were, as a rule, in such an early stage that there was no sputum and therefore no opportunity to look for bacilli. The points we wish to bring out are the value of these precautionary examinations as an aid to early diagnosis, and the importance of early diagnosis to patients.

ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD BY MEANS OF DIALYSIS

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AND

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There are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of removing from the body, at an adequate rate, the natural or unnatural substances whose accumulation is detrimental to life. In the hope of providing a substitute in such emergencies, which might tide over a dangerous crisis, as well as for the important information which it might be expected to provide, concerning the substances normally present in the blood, and also for the light that might thus be thrown on intermediary stages of metabolism, a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body, and again returned to the natural circulation without exposure to air, infection by microorganisms, or any alteration which would necessarily be prejudicial to life. The process may be appropriately referred to as "vividiffusion."

Essentially the method consists in passing the blood of an animal which has been made incoagulable by injection of hirudin from a cannula connected to an artery through a tube or a series of tubes, made of celloidin or other suitable dialyzing membrane, contained in a jacket filled with a saline solution or artificial serum,

and back by another cannula into a vein of the same animal. The tubes and cannulæ before connection are filled with a saline solution approximating to the composition of the blood, like Locke's or Ringer's solutions, which is displaced into the system when the circulation is established. Except that the blood-pressure falls somewhat, according to the proportion of the blood outside the body, the animal shows no immediate symptoms, and with due regard to asepsis, makes a rapid and complete recovery after an experiment that may last several hours. In one instance, where recovery was not aimed at, a dog anesthetized with chloretone was kept alive during a dialyzing period of sixteen hours with about one-third of its blood outside the body. At the end of an experiment the larger proportion of the blood in the apparatus may be driven back into the body by air-pressure or by means of a saline solution which is allowed to flow into the dialyzing tubes from a higher level and which thus drives the blood ahead of it into the body.

Many experiments have been made to determine the best form of apparatus combining maximum diffusing surface with minimum volume, absolute freedom from leaks, ease of construction, uniformity of flow, minimum exposures to surfaces of glass or other substance liable to favor clotting, etc. The most efficient type in use at present has thirty-two celloidin tubes of 8 mm. diameter, 40 cm. long, fastened by tying with a string to a system of glass tubes branching dichotomously, so that the flow of blood takes place horizontally twice in each direction through eight tubes in parallel. (An apparatus of this size can only be attached to animals of at least fifty pounds' weight.) Flattened tubes and other types are being tried, while very small tubes will undoubtedly prove valuable when the necessary time and trouble are not prohibitive.

Such an apparatus can obviously be used in the solution of many problems, both therapeutic and physiological, and is especially valuable in the latter case because, apart from the necessary anesthetic, the normal physiological condition is in nowise disturbed, as by bleeding to obtain large amounts of blood. Diffusible substances, present in only small proportion at one time, may be isolated in considerable quantities provided they are regenerated

in the body as fast as they are removed. Evidence of this has already been obtained in the case of the dialyzable (non-protein) nitrogen which is extracted in large quantities in prolonged experiments. Determinations by Van Slyke's method have shown a high proportion of nitrogen in the form of amino groups (NH_2), and experiments are in progress for the isolation of individual amino-acids by Fischer's esterification method. Several grams of the esters have been obtained by distillation in a vacuum of 1 to 16 mm. at temperatures from 70° to 180° C. Bases precipitated by phosphotungstic acid have also been obtained, but they apparently constitute a more complex mixture than those usually obtained in the digestion of proteins by acids, and the discovery of new bodies, possibly including polypeptids, seems probable.

Quantitative data have been obtained with a view to comparing the efficiency of the apparatus in the elimination of poisons with the natural kidney. Administering to a rabbit 1 gram of sodium salicylate, an extraction as rapid as 3 per cent. in one-half hour has been observed, which compares very favorably with the normal action of the kidneys; in the case of a dog with the same dose, using another apparatus, 4 per cent. was obtained in the first hour and a total of about 20 per cent. in sixteen hours. Better results may be confidently expected with an apparatus having more surface in proportion to the volume. Potassium iodide also passes through the membrane readily as does phenolsulphonephthalein. Of the substances naturally present in the body, sugar, phosphates, diastase, and other substances diffuse in notable amount.

Ethyl sulphide, $(C_2H_5)_2S$, which is so readily evolved from dogs' urine on the addition of lime-water or other alkali, may be obtained in like manner from the diffusate, showing that the mother-substance of this malodorous compound is freely eliminated by our apparatus.

A wide field of investigation is opened up by the use of this apparatus in a comparative study of the blood flowing to and from various organs with reference both to the substances which they extract from, or add to, the general circulation and to the special active principles (hormones, etc.) which may be present in their internal secretions. A beginning in this direction

has been made by attaching the apparatus to the portal vein, (four experiments), the blood of which gave by diffusion considerably more amino-acids (determined by Van Slyke's method) than that of the carotid. Work in this direction, as well as in the improvement of the apparatus for the various purposes above outlined and accumulation of the experience necessary along these lines, is being pushed actively forward. A full description of the apparatus, with directions for its use, together with the results, will appear in the January number (1914) of the *Journal of Pharmacology and Experimental Therapeutics*.

EXPERIMENTS ON THE CULTIVATION OF THE MICROÖRGANISM CAUSING EPIDEMIC POLIOMYELITIS

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Several attempts have been made to demonstrate under the microscope and to develop in artificial cultures the microörganism causing epidemic poliomyelitis, but hitherto unsuccessfully. Giersvold[1] cultivated certain micrococci from the cerebrospinal fluid, and Fox[2] a bacillus from the circulating blood of poliomyelitic patients, but both have now been discredited as causes of the disease. The discovery of the filterable nature of the causative agent independently by Flexner and Lewis[3] and Landsteiner and Levaditi[4] not only disposed finally of the claims made for the above-mentioned bacteria, but also discouraged renewed efforts at cultivation. Flexner and Lewis[5] noted and Levaditi[6] confirmed a clouding of serum bouillon by an aqueous Berkefeld filtrate of the central nervous tissues of poliomyelitic monkeys, but the phenomenon proved to be due to protein precipitation and not to multiplication of a living parasite. Proescher[7] has recently stained certain coccus-like bodies in films prepared from the central nervous organs of monkeys infected experimentally with the virus of poliomyelitis.

[1] Norsk Magazin f. Laegevidensk, 1905, iii, 1280.
[2] Dixon, Fox, and Rucker, Laboratory Report of the Department of Health of Pennsylvania, March 2, 1911.
[3] Jour. Amer. Med. Assoc., 1909, liii, 2095.
[4] Compt. rend. Soc. de biol., 1909, lxvii, 592.
[5] Jour. Amer. Med. Assoc., 1910, liv, 45.
[6] Presse Méd., 1910, xviii, 44
[7] New York Med. Jour., 1913, xcvii, 741.

The precise nature of these bodies has still to be worked out; apparently they have not yet been demonstrated in human nervous tissues, and similar bodies have been found in the nervous organs of animals experimentally infected with rabic materials. The comparatively large size of many of these coccoid bodies leaves it doubtful whether they can bear relation to filterable viruses.

The successful cultivation of spirochætæ, both parasitic and saprophytic, by Noguchi[1] provided the impulse for a renewed attempt at the cultivation of the microörganismal cause of poliomyelitis. The application by Noguchi of his method to the central nervous tissues derived both from human and from experimental (monkey) examples of poliomyelitis has yielded results of an entirely different order from those previously obtained. The results have already been described briefly in our Fifteenth Note,[2] and they will be described more fully in this place.

NATURE AND SOURCES OF MATERIALS

During the several years that epidemic poliomyelitis has prevailed in the eastern United States we have collected many specimens from affected human beings and monkeys. Portions of nervous and other organs were regularly set aside in 50 per cent. sterile glycerin in the refrigerator. Hence there were available for the cultivation tests both fresh specimens yielded by recent autopsies upon human beings and monkeys and material preserved for periods ranging from a few days to many months. The new experiments upon cultivation were begun during the summer of 1912, at which time many acute cases of poliomyelitis were being cared for in the Hospital of the Rockefeller Institute, where a number of autopsies were performed upon fatal cases. Thus the cultivation was carried out simultaneously upon fresh, sterile, or practically sterile (for ordinary bacteria) specimens derived from human beings and from monkeys experimentally inoculated, and upon glycerinated specimens from both sources.

[1] Jour. Exper. Med., 1911, xiv, 99; xv, 90; xvi, 199, 211.
[2] Flexner and Noguchi, Jour. Amer. Med. Assoc., 1913, ix, No. 5.

The material subjected to cultivation should be taken as soon after the death of the person or animal as possible, and should be obtained when possible in an aseptic condition. While any part of the central nervous system is suitable, the brain is to be preferred for the reason that it can be obtained more readily than the spinal cord or the intervertebral ganglia in an aseptic state. The dura covering one of the hemispheres having been seared with a hot instrument is incised with sterile instruments and the underlying cortex scrupulously exposed. From this a cube about $2\frac{1}{2}$ c.m. in diameter and extending into the white matter is excised and placed at once into a sterile dish. If desired, portions of the cerebellum may be obtained in a similar manner, and by removing the cerebral hemispheres and then lifting up the cerebellum the medulla may be exposed in an aseptic manner, so that portions may also be taken.

It is advisable to make the initial inoculation with fragments as well as with emulsions or with filtrates of the nervous tissues. The fragments are to be preferred since they require almost no manipulation. When, however, the original material is suspected or known to be contaminated, it is advisable to employ filtrates at the same time. The filtrates are prepared by grinding the nervous tissue in strength of about 5 per cent. with sand in distilled water or physiological salt solution. The resulting emulsion is shaken in the machine for about thirty minutes, after which the suspended matter is removed by centrifugalization and the supernatant fluid is pressed through a Berkefeld filter, N. or V.

METHOD OF CULTIVATION

The culture medium consists essentially of human ascitic fluid to which has been added a fragment of sterile fresh tissue. In contradistinction to the spirochætæ, for which sheep-serum water supplies a suitable medium, the microörganism isolated from the nervous organs of cases of poliomyelitis demands ascitic fluid. In obtaining the initial culture, the exclusion of oxygen is necessary, but it is not essential, as in the case of *Treponema pallidum*, that the inoculated tubes should be placed in an anaërobic jar; it suffices

to cover the liquid with a deep layer of sterile paraffin oil. In some instances, however, the initial growth can be obtained more certainly when the anaërobic jar is employed.

Test tubes measuring 1.5 x 20 cm. are chosen. Into each of a series a fragment of the usual size of sterile fresh kidney of the normal rabbit is placed. Next is added a fragment of corresponding size of the fresh or glycerinated cerebrum or other part of the brain or spinal cord, or even a Berkefeld filtrate. Upon these are poured about 15 c.c. of sterile ascitic fluid and finally about 4 c.c. of the sterile paraffin oil. The ascitic fluid must have been originally sterile, since sterilization by fractional heating or filtration renders it unsuitable. The control tubes consist of the ascitic fluid and kidney fragment without brain tissue and ascitic fluid plus brain tissue without the kidney fragment. It is best to prepare two sets of the cultures, one to be placed in the anaërobic jar and the other kept outside. The incubation is conducted at the temperature of the thermostat, namely, at 37° C.

The culture tubes in the anaërobic jars should not be disturbed for from seven to twelve days, while those not within the jar may be inspected daily. Any tube showing marked turbidity, coagulation, or gas production within one or two days may be set aside as grossly contaminated. The tubes which remain clear or show only slight turbidity may none the less be contaminated. To exclude contamination small quantities of the medium are removed with pipettes and stained for bacteria in the ordinary way and cultivated upon the usual solid or fluid media. Obvious bacteria in the films as well as any growth taking place in the ordinary media in the presence of air may be put down as contaminations and the tubes containing them discarded.

Gross contaminations having been excluded, the peculiar microorganism obtained from the poliomyelitic nervous tissues exhibits the following growth characters. At the expiration of about five days' incubation a faint opalescence appears about the fragments of tissue at the bottom of the tube. This opalescence can be gradually diffused through the tube by gentle shaking (agitation), in the course of which it is observed that the turbidity about the tissues was really greater than was at first apparent. The control

tubes when not grossly contaminated either remain perfectly clear or a slight granular precipitate of washed-out particles of tissue forms about them. The two appearances are quite distinct and become more pronounced after another period of three to five days, during which time the opalescence first described extends into the upper portion of the medium, while in the controls the precipitate gathers more and more at the lower end of the tubes. At the expiration of ten or twelve days the diffuse opalescence of the medium in which growth has been observed to take place begins to diminish as sedimentation sets in, during which minute irregular particles form, heavy enough to fall slowly to the bottom of the tube.

Cultivation may also be performed in a solid medium, consisting of ascitic fluid and sterile rabbit tissue, to which a suitable quantity of 2 per cent. nutrient agar has been added in order to produce a solid mixture. The melted agar, cooled to a temperature of 40°, is mixed with the ascitic fluid in the tube containing the fragment of tissue, also previously heated to 40°. After cooling and solidification the medium should be sufficiently firm to maintain its stability. In this medium an initial growth, aside from contaminations, from poliomyelitic material has never been obtained, but once growth has been secured in the fluid medium it is possible, but not in all instances, to transmit it to the solid medium. Often successful transfer from the fluid to the solid medium is not accomplished until about the third generation of the growth has been obtained in the fluid medium. The changes indicative of growth in the solid medium begin about the fragment of tissue and appear first as a diffuse opalescence which gradually aggregates into visible grains of minute size that are recognized as colonies. Several days are usually required before this initial change in the medium becomes apparent. The rapidity with which it does become apparent is affected by the generation of the culture, and hence by its adaptation to the medium. Gradually the opalescence rises in the medium within the tube, until it reaches within about 3 cm. of the surface of the medium, at which a sharp line of demarcation appears. When the number of colonies developing is large the individuals are so minute as to give a diffuse

grayish appearance to the medium, which requires a lens to bring out the separate colonies. When the number of colonies developing is smaller they may reach a diameter of about $\frac{1}{3}$ mm. and hence become visible as such to the naked eye, to which they appear round in shape and grayish white in color. Under favorable conditions the opalescence indicating growth about the tissue fragment becomes apparent at the end of forty-eight hours and distinct after seventy-two to ninety-six hours, although several days may be required before the ascent of the growth to the line of demarcation, at which the presence of oxygen brings about a cessation of development.

The description just given relates to cultivation with fragments of fresh central nervous organs in the ascitic fluid and in the presence of sterile rabbit tissue. It is, however, possible to secure cultivation even in the absence of the rabbit tissue. For this purpose a somewhat larger fragment of the poliomyelitic brain is placed in the tubes containing the ascitic fluid, which is then covered with the layer of paraffin oil. After incubation at 37° the initial growth takes place, but with less constancy than when the rabbit tissue is also present. When it occurs the growth is usually so slight that the opalescence remains absent or nearly so, and it becomes necessary to transplant into a medium containing fresh rabbit tissue to establish its existence. It is possible also to substitute a Berkefeld filtrate prepared from the brain or even sheep-serum water, with rabbit tissue, for the ascitic fluid, but the growth is less uniformly or abundantly obtained.

Once the initial growth from any of the sources mentioned has been secured it is as a rule possible to obtain subcultures by transplanting about 0.2 c.c. of the original culture per tube into the next series. Since the initial growth begins about the tissue at the bottom of the tube it is advisable to take the fluid for transplantation from this location. Subcultures are obtained more constantly in the fluid than in the solid medium. Hence, growth will sometimes appear in the former and not in the latter. Once the microörganism has been adapted to the conditions of artificial cultivation, transplantation to the solid medium may be effected. The adaptation is indicated by a more rapid and abundant growth in the fluid

medium, and its occurrence is promoted by the presence of fresh sterile tissue and is prejudiced by its absence. Among the monkey tissues was one specimen which had been glycerinated for nine months, and from which a growth was obtained with a Berkefeld filtrate.

MORPHOLOGICAL CHARACTERS

Uncontaminated cultures of the microörganism from the various human and monkey sources already mentioned possess common morphological and staining characters. Fluid cultures viewed under the dark-field microscope exhibit among the innumerable dancing protein and other granules present minute bodies, globular in form, hanging together in short chains, pairs, and small masses, devoid of independent motility and distinguishable with difficulty as a special class among the indefinite granules present. Stained preparations, on the other hand, bring out unmistakable microorganisms grouped in the three ways stated and of very minute size. Staining may be accomplished with more or less difficulty in several ways, but the two methods which have thus far yielded the most satisfactory results are those of Giemsa and Gram.

The Giemsa stain may be applied in two ways according as a rapid or a somewhat slower but better result is desired. In the first the film, either upon a slide or a cover-glass, is allowed to become air-dry, when it is fixed over the flame, and several drops of Giemsa solution are dropped upon it and diluted with about twenty drops of distilled water. After gentle mixing of the dye and water the preparation is held over the flame until a trace of vapor rises. Care is exercised to avoid boiling. The preparation is then washed in a stream of distilled water, pressed between blotters, and dried. This method does not yield uniform staining or constancy of shade, but is useful for rapid examinations. The second method is the one usually employed. The film having been air-dried is fixed in methyl alcohol for about an hour, washed in distilled water, and then immersed in the solution containing one drop of the stain per cubic centimeter of distilled water, in which the film remains for from two hours to twelve to fourteen hours (overnight). Gram

stain is applied in the usual way, using gentian violet as the dye and safranin as the counter-stain. The microörganism behaves variably toward the Gram stain. When the medium in which it is grown contains peptone, it retains the stain more assiduously than when it is devoid of that substance. Then the intensity with which the Gram stain is retained varies with the age of the culture. The older the culture the more firmly the gentian violet is held. While the grouping is of course identical whichever stain is employed the apparent size of the microörganism is affected by the dye. When the gentian violet is retained the individuals appear larger than they do with either the safranin or the Giemsa stain. Loeffler's alkaline methylene blue, carbol-fuchsin and carbol-gentian violet all stain the microörganism slightly or without affording sharp differentiation. The microscopic appearances of the microorganism vary somewhat according to whether the growth is in a fluid or solid medium and peptone is present or absent. Peptone and possibly other constituents of the bouillon render the microorganisms somewhat larger as well as enable them to retain more firmly the Gram stain.

Films prepared from the lower layer of the ascitic fluid culture about the sterile rabbit tissue and stained by Giemsa solution reveal the presence of a variable number of minute globoid bodies, arranged in pairs or short chains, or in small aggregated masses. In the fluid culture the pairs and chains predominate. According as the staining operation was carried out by the rapid or slower method, the globoid bodies assume a bluish or a violet color; rarely they present a red tint. Since the most uniform results are obtained by the slower method of staining, it may be considered that the violet coloration is the normal. The individual microorganisms being considered average about 0.2μ in diameter, the limits of visible bodies being 0.15μ to 0.3μ Possibly still smaller individuals exist that exceed the limit of visibility.

Within the solid cultures the microörganism develops not as chains but as pairs and aggregated groups. The arrangement is very readily ascertained by compressing a fragment of the agar between two slides, which are afterward separated. The resulting films having been stained in the usual manner by Giemsa or Gram

solution, the minute particles of agar adhering to the glass will frequently exhibit colonies, of which the members are sufficiently separated to expose the grouping. In the Gram-stained films the bodies are somewhat coarser than in the Giemsa-stained ones. In young agar cultures the Gram-stained bodies are partly purple and partly pink, while in older cultures almost all appear purple.

After a somewhat variable period, and generally from ten days to three or four weeks after the maximum growth has been obtained, certain metamorphoses or degenerations set in. Probably the enlarged and irregular stained bodies are to be viewed as degenerations, while the minute fragments just at the limit of visibility may possibly represent a metamorphosis into a minuter variety with which submicroscopic forms may be associated. When the conditions of culture are unfavorable, as, for example, when the brain extract or other medium without sterile tissue is employed, this supposed metamorphosis appears to arise earlier, and indeed within the first few days of growth. Subcultivation from one of the altered cultures or from their Berkefeld filtrates yields frequently but not uniformly new developments of the visible microörganisms. The important question, as to whether the cultures just mentioned contain actual ultramicroscopic forms of the microörganism, or whether the failure to detect the visible forms is due chiefly to dilution, must remain for the present undecided. What is certain, however, is that the globoid organisms are capable of passing through Berkefeld filters which exclude the usual test bacteria (*e. g.*, *M. prodigiosus*). Cultures from the Berkefeld filtrates should always be made in the ascitic fluid tissue medium, as in the case of the initial growth.

The film preparations stained by the Giemsa and especially by the rapid method sometimes show the globoid organisms surrounded by a zone either faintly tinted or colorless, that may equal in width the diameter of the individual microörganisms. Single bodies, aggregated groups, or chains may be thus enveloped. The nature of the material composing the zone is unknown, as is also whether it represents an independent part of the organism (capsule?) or is derived from the culture medium.

INFECTION OF MONKEYS

The microörganism described is present so constantly in the central nervous tissues of affected human beings and monkeys that a strong presumption exists to the effect that it bears some relationship to epidemic poliomyelitis. It is sufficiently obvious that whatever they may ultimately prove to be, so far as we now know, the globoid bodies are not common pathogenic or even saprophytic microörganisms. Whether the bodies are limited to the central nervous organs or occur more widely distributed in the body of infected human beings and monkeys is still to be determined. The question which presses at the moment is whether the cultures are capable of setting up in monkeys clinical and pathological states corresponding with those characteristic of experimental poliomyelitis. Before proceeding to describe the inoculation experiments, it may be well to point out that apparently the globoid bodies are highly parasitic microörganisms. In view of this circumstance it may readily happen that they may quickly lose pathogenic properties in artificial cultures. There are of course several instances known among the bacteria and spirochætæ of which this circumstance is true. We were therefore prepared to encounter difficulties in the way of infecting monkeys with cultures. It is necessary to recall the difficulties surrounding the original implantation of highly infected human poliomyelitic material upon monkeys in order to have emphatically presented the probable obstacles that stand in the way of the successful accomplishment of the infection of monkeys with the cultures.

Two series of inoculations were made. In one the cultures derived from the nervous tissues of monkeys and in the other from human beings directly were separately inoculated into Macacus monkeys. The inoculations were made either into the brain or into the sciatic nerve and peritoneal cavity simultaneously.

The implantation upon monkeys of the virus contained in the original human nervous tissues is admittedly difficult. When filtrates are inoculated failure usually follows. When emulsions are employed, infection occurs in from about 50 to 100 per cent. of

the instances, probably depending upon the variation in the degree of infectivity of the original virus. The human strains of the virus are less infectious for monkeys than the adapted or so-called monkey strains, a fact that is the more significant as respects the successful inoculation of cultures derived directly from human tissues. None the less cultures derived directly from human tissues as well as from the highly adapted M A strain, that has been propagated in monkeys for four years, were successfully inoculated upon rhesus monkeys. The resulting infections were secured with cultures in the fifth, sixth, and even the eighteenth and twentieth generations.

The inoculation experiments showed unmistakably that the injection of the cultures is followed by the appearance of the clinical symptoms and pathological effects characteristic of experimental poliomyelitis in the monkey. The two methods of inoculation now chiefly practised with the usual suspensions or filtrates of nervous tissues were employed successfully with the cultures. The essential results are identical whether the cultures are inoculated into the brain or simultaneously into sciatic nerve and peritoneal cavity. The inoculation of the cultures produces in monkeys no direct effect. Immediately after injection the animals appear normal and they remain apparently in this condition for an incubation period which may be as brief as forty-eight hours, but commonly endures for one to several weeks, at the expiration of which the usual symptoms of excitement, tremor, weak, and then paralyzed muscles succeed one another. Death may arise from prostration, convulsions, or paralysis of the respiration, although in most instances it was artificially hastened by etherization.

The central nervous tissues of the monkeys may be employed for recultivation of the microörganism inoculated, or for transmitting the experimental affection to still other and probably an indefinite series of monkeys. This transmission can be accomplished either with emulsions or Berkefeld filtrates of the fresh or glycerinated organs. Since the experimental disease is accurately reproduced in this manner, it follows that not only the cultures but the nervous tissues infected with them possess the distinctive disease-producing properties of the virus of poliomyelitis as commonly understood.

The local effects of the cultures vary with the inoculation site

and the dosage. Unless secondary infection arises from the outside, the intrasciatic and intraperitoneal inoculations cause no considerable reaction, while the intracerebral infection leads to the formation of a small cyst, in which the introduced microörganism may or may not be readily discoverable in film preparations. If relatively few of the microörganisms are inoculated, they tend to disappear from view; while if many are introduced, they are readily detected, either lying free or enclosed in emigrated polynuclear or mononuclear cells. When pyogenic micrococci enter from the skin, the local lesion tends to be larger, and to contain many pus cells, and the two microörganisms may appear side by side, both without and within cells. When an excess of the mixed fluid and solid cultures is injected into the brain, the local effect is also more severe and many leukocytes may be called out by the positively chemotactic elements contained within the medium. The action of contaminated cultures is less readily interpreted than are the effects of pure cultures; but any doubt may be removed by preparing a Berkefeld filtrate from the local lesion and portions of the medulla, spinal cord, and intervertebral ganglia, which is to be employed for inoculation.

The disappearance of the microörganism from the inconspicuous local lesions probably results from a general diffusion throughout the nervous organs and restricted multiplication at the site of injection. The microörganism can indeed be recovered in cultures from any part of the central nervous system, and is best recovered from the intact cerebral hemisphere, where it usually exists in a pure state and is readily accessible under aseptic conditions.

RELATION OF THE MICROÖRGANISM TO NERVOUS TISSUES

The microörganism, the cultures of which have been described, can be detected in film preparations and in sections prepared from the central nervous organs of human beings who have succumbed to poliomyelitis and of monkeys subjected to inoculation with the ordinary virus or with cultures. A special technique which has been devised by Noguchi is required for the demonstration. With

these methods the minute microörganism has been demonstrated in the films in eighteen out of nineteen specimens of glycerinated human nervous tissues. It was detected regularly lying between cells and in some instances within the cytoplasm of cells, some of which were nerve cells. The microörganism appears invariably in pairs or small aggregated groups and never in chains. The demonstration of the microörganism in sections is far more difficult, but it has been detected in a few instances in the interstices of the tissues and in the protoplasm of cells. The detection of the organism in film preparations and in sections has been accomplished also with nervous tissues derived from monkeys inoculated at one time with the ordinary virus, at another with cultures. In this case also the microörganism is more readily brought out in film preparations than in sections. The grouping is identical with that present in the specimens of human origin.

RÉSUMÉ

From the facts presented it follows that by employing a specially devised method there has been cultivated from the central nervous tissues of human beings and monkeys the subjects of epidemic poliomyelitis a peculiar minute organism that has been caused to reproduce the symptoms and lesions of experimental poliomyelitis. The microörganism consists of globoid bodies measuring from 0.15 to 0.3μ in diameter, and arranged in pairs, chains, and masses, according to the conditions of growth and multiplication. The chain formation takes place in a fluid medium, the other groupings in both solid and fluid media. Within the tissues of infected human beings and animals the chains do not appear.

Only the exceptional cultures possess the degree of pathogenicity sufficient to cause specific infection, and the production of experimental poliomyelitis. A pathogenic strain may be effective at different and even remote generations, and a non-pathogenic strain may lack pathogenicity even in the second generation. This important fact indicates strongly that the pathogenic effect is not due to mere mechanical carrying over into the cultures of an

invisible parasite or virus with which the cultivated microörganism is accidentally associated. If such accidental association were the cause of the experimental disease produced by the cultures in monkeys, it would display itself preferably in the first generations and without reference to the strain of the visible microörganism. On the other hand, in this fluctuation of pathogenicity the cultures imitate the action of the virus as contained in human materials, namely, nervous tissue, secretions from the nasopharynx, and intestinal washings, in which the virus, either known or believed to be present, may yet fail to be demonstrated by reason of the want of infectious power for monkeys or for the particular monkey inoculated in a given instance. Moreover, it is a common experience in bacteriology to find even among the ordinary bacteria lack or rapid loss of virulence among saprophytic cultures, while virulence is not only retained, but may be increased in rapid passages from animal to animal. In view of these considerations it would appear that an etiological relationship has been shown to exist between the cultivated microörganism and epidemic poliomyelitis as it occurs in human beings or in monkeys.

DISCUSSION

Dr. W. H. Park: I would ask Dr. Flexner if in passing cultures of this virus through porcelain filters the organisms can be recovered from the sediment? If so, we may have to revise some of our notions about filterable viruses.

Dr. M. J. Rosenau: Has any growth been obtained from the filtrate?

Dr. Frank Billings: I would like to ask if Dr. Flexner or any one else present has any evidence that poliomyelitis may occur in the fetus *in utero?* I ask the question because I think I have seen such a case.

Dr. Flexner: We have not looked into the question raised by Dr. Park for lack of time; but we know that the organism is present in small numbers in the sediment left in the filter. The organism can be cultivated from the filtrate, but with some uncertainty. I have heard of no such case as that mentioned by Dr. Billings.

THE MODE OF TRANSMISSION OF POLIOMYELITIS

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From a practical point of view the mode of transmission is the most useful single factor in combating a disease. The health officer would prefer to know the precise mode or modes of transmission of any disease rather than its cause, or pathologic anatomy, or even its treatment. Hence a large amount of work has been done to determine how the virus of poliomyelitis leaves the body, how it enters its victim, and the route it takes from one person to the next. Despite all the thought and work that has been focussed on this problem, the mode of transmission of poliomyelitis remains an open chapter, and although much light has been thrown on the subject, the present state of our knowledge does not permit of dogmatic, much less final statements.

There are two avenues of approach to a problem of this sort; one, through epidemiologic field studies, and the other through laboratory research work. Both these trails have been blazed. Much of the epidemiologic work has given conflicting results, and much of the laboratory work has likewise been confusing. The evidence obtained from the field and that from the laboratory, however, do not have an equal standing before the court. The fallibility of epidemiologic evidence has long been recognized. Sanitarians who have had a long experience know full well that it has always been necessary to revise the chapter on the epidemiology of a disease as soon as its mode of transference is discovered. All those who have collected field data are fully aware of the pitfalls. Errors are unavoidable from the very nature of the circum-

stances; the personal equation and also the limitations of the investigator often warp or dwarf the important facts. In any event, the enormous mass of data collected by careful investigators in the field is perplexing and difficult to analyze. Even if the epidemiologist has the detective instinct of a Sherlock Holmes, and the statistical genius of a Karl Pearson, he may be wholly carried off the track by the missed cases, and by the carriers, or by an incomplete knowledge of unusual forms of the disease, or by unknown factors in its etiology. On the other hand, the exact observations from the laboratory often throw a flood of light on our field work, and when the two are correlated we have real and useful additions to our knowledge.

There are many theories to account for the spread of poliomyelitis. The chief ones may be summarized under four headings: (1) That it is a "contagious" disease, communicated directly from person to person through the secretions from the mouth and nose; (2) that it is an insect-borne disease; (3) that it is conveyed through dust, and (4) that it is an alimentary infection, the virus being taken in with food and drink and absorbed from the digestive tube. There is evidence from the field and from the laboratory to support each one of these theories. These four theories, however, do not include all the views brought forward to explain the mode of transmission of infantile paralysis. For example, the hypothesis has been expressed that the disease is transmitted to man from lower animals, particularly domesticated animals, but there has been no convincing demonstration that the infection occurs naturally in any other animal than man.

In view of the uncertainty concerning the mode of transmission of poliomyelitis it is worth while to take stock of our knowledge of this subject. I have therefore briefly summarized the evidence pro and con.

That anterior poliomyelitis may be a contagious disease was first announced by Wickman, of Sweden, whose epidemiologic investigations upon the subject are now classic. Wickman formulated a new symptomatology; his greatest contribution to the subject was perhaps the discovery that abortive cases of the disease occur. These mild, and hitherto unrecognized clinical forms, shed

an entirely different light on the epidemiology. Wickman brought forward strong evidence in support of the view that the disease was transmitted directly from person to person, especially through the abortive or missed cases, as well as through suspected carriers.

The theory that infantile paralysis is a "contagious" disease was the first, and is the most natural explanation to account for its spread. In many respects infantile paralysis resembles epidemic cerebrospinal meningitis, with which disease it is, in fact, sometimes confused. Flexner has emphasized the resemblance between the two infections, and has been an able and valiant champion of the view that the virus in both these diseases leaves the body in the secretions from the mouth and nose and enters the victim through the same channel. Corroboration of this view has come especially through the work of the Swedish investigators, Kling, Pettersson, and Wernstedt, who claim to have demonstrated the virus in the secretions from the nose and throat, not only in cases during the acute stage, but also during various stages of convalescence, and even in healthy carriers. Furthermore, Osgood and Lucas demonstrated the virus in the mucous membrane of a monkey, five and a half months after recovery from the experimental disease and recently they recovered it from a chronic carrier in man. Kling claims to have found the virus in the nasopharynx up to seven months in a few human cases. Finally, it is possible to infect monkeys simply by placing the virus on the uninjured mucous membrane of the nose and throat. The evidence, therefore, that we are dealing with an infection that leaves the body in the secretions from the nose and throat, and enters by the same channel, is strong, both from epidemiologic studies and from laboratory investigations. That this evidence, however, is not conclusive, may be gleaned by a little closer consideration of the facts.

It is important, first of all, to remember that we have no clear-cut criterion by which to judge what is and what is not anterior poliomyelitis. When the symptoms are characteristic and the lesions typical we are justified in making a definite diagnosis. In any critical case, however, further corroboration must be had by transferring the virus from monkey to monkey in order to demonstrate that we are, in fact, dealing with a communicable infection

capable of reproducing itself. When we apply this criterion to some of the work that has been reported, to support the view that infantile paralysis is a "contagious" disease, we find the evidence not as strong as the conclusions of the experimenters would lead us to suspect. The mere fact that an animal has an acute paralytic affection, associated with perivascular infiltrations, degeneration of the neurons, and occasional hemorrhages into the cord, is not enough, in the present state of our knowledge, to justify us in labelling it poliomyelitis. The criterion in critical cases must be the power of the virus to reproduce itself and repeat the symptoms and lesions of the infection through succeeding generations.

There has been a long series of negative results in attempts to demonstrate the presence of the virus in the secretions from the mouth and nose. Strauss, Rosenau, Sheppard and Amoss, Flexner, and also Anderson and others, have all reported failures in this regard. These negative results have a certain degree of positive significance, for if the usual means of transmission of the disease is through the secretions from the mouth and nose we should not have such great difficulty in demonstrating its presence in these secretions. Only Kling,[1] Pettersson, and Wernstedt have found it comparatively easy to make this demonstration. These investigators believe that they have established the important fact that carriers occur, and are several times more numerous than the frank and abortive cases of poliomyelitis combined. Yet Flexner, Clark, and Frazer report only one positive result out of numerous trials. They succeeded in demonstrating the virus of poliomyelitis in the washings from the nasopharynges of the parents of a child suffering with poliomyelitis. The parents, however, showed no symptoms of illness.

The virus of anterior poliomyelitis is widely diffused throughout

[1] Kling found it comparatively easy to demonstrate the presence of the virus in the washings from the mucous membranes. Thus he found that 78 per cent. of the monkeys contracted the disease after inoculation with water in which the mucous membranes of poliomyelitis cadavers had been rinsed. The virus was also found almost constantly in the secretions from the nose and throat of acute poliomyelitis patients. These results are so much at variance with the results obtained by American investigators that the question has arisen whether we are dealing with the same virus in America as that found in Sweden, or whether the virus has marked differences in virulence, or whether there is some experimental error or more likely an incorrect interpretation of results.

the body. It has been found in greatest virulence and concentration in the spinal cord of infected persons and animals. The virus is also quite constantly present in the brain and other organs and tissues as, for instance, the mucous membrane of the nose and pharynx, the mesenteric glands, the axillary and inguinal lymph nodes, and even in the blood and the cerebrospinal fluid. Recently the virus has been demonstrated in the mucosa of the intestinl tract, and finally in the feces. It is therefore no surprise that a virus with such a wide distribution and so generally diffused throughout the body may occasionally be found in the secretions from the nose and throat. These facts make us hesitate to conclude that infantile paralysis must be a contagious disease, simply because it has been demonstrated experimentally that the virus may be found occasionally in the secretions from the nose and throat; it would be just as logical to conclude that the disease in its spread resembles typhoid fever because the virus has been demonstrated in the mucous membrane of the digestive tube and has also been found in discharges from the intestines.

There are other difficulties which must be met before we can accept as a proved fact that infantile paralysis is a contagious disease. Careful and masterly epidemiologic investigations of poliomyelitis have been conducted by the Massachusetts State Board of Health extending over a period of five years. The results of these studies were summarized by Dr. Mark W. Richardson, who plainly brought out the fact that the disease, as observed in Massachusetts, does not have the ear-marks of a contagious disease. The disease prevails in rural rather than under urban conditions. In fact, it shows little tendency to invade cities, and when it does enter the city, it does not strike the crowded, congested portions of the city. All other contagious diseases spread through the secretions from the mouth and nose; epidemic outbreaks have been observed in crowded sections of cities, in asylums, hospitals, jails, on shipboard, and similar places where the spread of infection by contact is favored. This is the case with scarlet fever, diphtheria, measles, mumps, whooping cough, influenza, common colds, pneumonia, and finally cerebrospinal meningitis. Cases of infantile paralysis in all stages of the disease have been taken into the hos-

pitals, orphan asylums, children's homes, reformatory schools, and other institutions in the Commonwealth, but in no instance during the five years in which the disease has been studied has it ever spread under these circumstances.

The seasonal prevalence, furthermore, of infantile paralysis does not suggest the seasonal prevalence of the diseases spread by contact through secretions from the mouth and nose. Almost all such diseases, including cerebrospinal meningitis, occur more particularly during the cold months of the year, whereas the prevalence of infantile paralysis is more marked during the summer months.

The curve of seasonal prevalence of infantile paralysis corresponds more closely with that of typhoid and the diarrheal diseases than it does with the group of infections spread through the secretions from the mouth and nose. Typhoid has its season of maximum prevalence during the warm weather. Water-borne epidemics are apt to occur in the colder months of the year, and milk outbreaks may take place at any time. "Normal," or residual typhoid is a warm-weather disease and corresponds in this regard with cholera, dysentery, and the infantile diarrheas, and other intestinal infections The only other group of diseases which prevail especially during the warm weather are those which are insect-borne. Yellow fever stops with the first frost. The most pernicious form of malaria (estivo-autumnal) extends into the autumn, but the autumn of tropical regions is warm, rainy, and favorable to mosquito life. The season of maximum prevalence of the insect-borne diseases corresponds, of course, to the season of maximum prevalence of insect life, namely, the summer.

It has long been evident to the student of epidemiology that the group of "contagious" diseases spread through the secretions from the mouth and nose occur throughout the entire year, but prevail especially during the colder months. On the other hand, there are two groups of disease having their maximum seasonal prevalence during the warm weather, namely, the intestinal infections and the insect-borne diseases. Of these two groups of summer diseases the insect-borne group disappears almost to the vanishing point in temperate latitudes with wintry climates, whereas the intestinal

diseases continue to smoulder all winter long, with occasional exacerbations, and sometimes even with outbreaks of epidemic proportions. These are generalizations that may not be applicable to a specific case. When we study the seasonal prevalence of infantile paralysis in all parts of the world, however, we find a summer prevalence, sometimes extending into the fall, but dying down almost out of sight during the winter and spring. So far as we may judge, then, from the seasonal prevalence of this infection, it corresponds more closely with that of the insect-borne type than any other group of diseases.

If poliomyelitis is a contagious disease, then we must construct secondary theories to fit certain known facts in its distribution, seasonal prevalence and age predilection—facts which are at variance with this theory. The bulk of the cases of poliomyelitis may be very mild, and only those cases perhaps are recognized that reach the threshold of clinical observation. A similar situation would be presented if we knew diphtheria only by the cases of postdiphtheritic paralysis. Each case of poliomyelitis, in accordance with the assumption that it is spread by contact, would be surrounded by a number of healthy carriers, but serious epidemics do not occur because the infected persons are not very susceptible. Why epidemic outbreaks should occur in rural conditions and not in the congested parts of cities is, however, not explained by this assumption. The assumed barrier of resisting individuals apparently isolates the case, but, in fact, favors the spread of the infection. It seems to be a general rule that a region where the disease has been epidemic is spared further outbreaks later. This phenomenon may be explained by assuming that a large part of the population has become immunized by having had the disease in an attenuated and unrecognized form. It is further assumed that in rural districts there is not the same opportunity perhaps to acquire immunity, and when an epidemic occurs it is liable to run an exceptionally severe course. The loopholes in these conceptions are evident to students of the disease, but it is an interesting speculation that deserves careful consideration and further study.

That infantile paralysis may be an intestinal infection has not been given the consideration that it deserves. In addition to a

suggestive seasonal prevalence, there is the age incidence and gastro-intestinal symptoms which often usher in an attack; furthermore, we have the fact that monkeys may be infected by feeding, and the further important fact that the virus has been demonstrated in the intestinal mucosa, and even in the discharges from the bowels. No convincing outbreak of infantile paralysis has ever been associated with water, milk, meat, or other article of diet. Furthermore, we would expect a somewhat different epidemiology if food were a medium in transmitting the virus. The inherent unreliability of epidemiologic data, especially of a disease such as infantile paralysis, has already been noted, and the possibility of the virus entering by the digestive tube should be borne in mind by investigators. It took a long time to learn that milk may convey scarlet fever and other infections, and that pork may be responsible for trichinosis.

There has long been a suspicion that man contracts infantile paralysis from the lower animals. Hill incriminates horses. Thus, colts in Minnesota have suffered with a disease clinically like poliomyelitis, and the hypothesis has been proposed that the virus is spread through the intestinal discharges of horses, which, drying, fly about as dust. A number of other students have associated it in one way or another with horses. Joest has described in detail the lesions of a disease of horses known as *Bornasche's Krankheit*, which has a similarity to poliomyelitis. Langhorst considers a possible relationship with the dog and cites two cases, in one of which the patient was bitten by a dog; the other patient was licked by a dog, and at the same time had a few scratches on his hand. In both cases the diagnosis of rabies was not excluded. In fact, there are many striking resemblances between rabies and poliomyelitis. All laboratory investigators who have worked with these two diseases have been struck with this resemblance. Both diseases are acute paralytic affections. The virus in both diseases is found in its greatest concentration and virulence in the central nervous system, but is also widely diffused throughout the body. The virus of both infections is filterable, and in both affections the brunt of the lesions fall on the neurons of the central nervous system. There are other similarities between the two diseases

which should be borne in mind, especially when studying the possible relationship between poliomyelitis and dogs.

Many observations have been made in Massachusetts and elsewhere of paralytic diseases of domestic animals occurring about the same time as poliomyelitis in man. Such paralytic diseases are common among pigs and also chickens, as well as horses, dogs, cats, etc. P. Roemer reported a paralytic disease in guinea-pigs which occurred among animals in his laboratory. The guinea-pigs died of a paralysis which has some resemblance to infantile paralysis. The infection is transmissible from guinea-pig to guinea-pig by inoculation; the virus is found to be non-bacterial, and filterable; the incubation period is from nine to twelve days; the symptoms are flaccid paralysis, usually of the hind legs, with involvement of the bladder. Microscopically there is also a resemblance in the lesions of these guinea-pigs and those of poliomyelitis in man and monkeys. Roemer, however, does not claim, and there is nothing to indicate, that this paralytic disease of guinea-pigs is identical with poliomyelitis. Neustaedter has recently noted a paralytic affection of guinea-pigs that were kept in a cage under some monkeys with experimental poliomyelitis. The evidence that any of these paralytic diseases were genuine instances of true infantile paralysis is far from convincing.

Animals suffer with many paralytic diseases, the etiology of a few of which are known, but most of which are pathologic puzzles. The mere fact that an animal has an acute paralytic infection, with perhaps suggestive lesions in the cord, is not sufficient basis for concluding that we are dealing with poliomyelitis. All attempts to transmit the virus of infantile paralysis to lower animals except the monkey have failed. Theobald Smith, Flexner, and others have made numerous attempts to carry on the paralytic diseases of pigs, chickens, and other animals without success. Therefore, while it is fairly possible that some of the lower animals may suffer with poliomyelitis, perhaps in a clinically unrecognized form, and while it is possible that man may contract the infection from lower animals, the possibility is only an assumption and lacks evidence.

Another theory to account for the spread of infantile paralysis is that it is dust-borne. Hill's observations of dust and its relation

to the disease in Minnesota have already been referred to. The Massachusetts State Board of Health, during the five years of its epidemiologic studies, also considered the possibility of dust as a medium of conveying the virus, without, however, discovering any particular relationship between dust and the disease. The most suggestive evidence comes from Neustaedter and Thro, who claim to have induced the disease in monkeys by inoculating them with the dust found in sick-rooms. If the virus leaves the body in any considerable amount in the secretions from the mouth and nose, it is quite conceivable that the dust of the sick-room may contain the virus, for we know that, under certain circumstances, it retains its viability for months. Poliomyelitis does not have the characteristics of a dust-borne disease, or even of an air-borne infection, and this hypothesis has therefore been given scant credence.

The possibility that poliomyelitis may be a wound infection has been kept in mind in the investigations made by the Massachusetts State Board of Health. No particular relationship between wounds and the disease has been made out. The resemblance between infantile paralysis and rabies has already been discussed, and the fact is plain that monkeys may be inoculated through wounds; in fact, it is possible to cause the disease in the monkeys in the greatest possible varieties of ways.

Some of the reasons for considering poliomyelitis an insect-borne disease have been published in some detail in another publication, and need not now be recounted. The epidemiologic evidence collected by Brues and Sheppard, and summarized by Richardson, pointed toward the stable-fly, *Stomoxys calcitrans*. The successful experiments of Rosenau and Brues, soon corroborated by Anderson and Frost, incriminate the stable-fly as a factor in the transfer of the virus. The seasonal prevalence, the rural distribution, and other facts concerning the disease are explained on this theory. On the other hand, the experimental facts lack further corroboration, and, moreover, these facts have not been translated from monkey to man, and we are not justified in doing so until further studies, which are now being made, are available. Schuberg and Kuhn have recently demonstrated that a number and variety of infections

may be transmitted by means of the stable-fly. In their experimental work they obtained positive results with relapsing fever, anthrax, southwest African horse sickness (*Pferdesterbe*), and epithelioma of fowls (*Hühnepocken*).

Howard and Clark conducted a series of experiments on insect transmission with the virus of poliomyelitis, at the Rockefeller Institute, with very interesting results. It was found that the domestic fly, *Musca domestica*, can carry the virus of poliomyelitis in an active state for several days on the surface of the body, and for several hours within the gastro-intestinal tract. These experiments were made by permitting the flies to feed on the virus, then killing the insects, grinding up their bodies, filtering, and injecting the filtrate into monkeys. Howard and Clark found that mosquitoes (*Culex pipiens*, *C. sollicitans*, and *C. cantator*) did not take up and maintain in a living state the virus from the spinal cords of monkeys. Negative results were also obtained with lice (*Pediculus capitis* and *P. vestimenti*). The experiments with lice were designed to simulate natural conditions, but it was found that these insects did not take the virus of the blood of monkeys or maintain it in a living state. The bed-bug (*Cimex lectularius*), however, gave positive results in that it was found in one experiment to have taken the virus with the blood from infected monkeys and maintained it in a living state within the body for a period of seven days. When we consider that the virus exists in the blood of monkeys in a very dilute state, for it requires a number of cubic centimeters of blood to infect another monkey, we are almost driven to the conclusion that the virus must have become concentrated (grown?) in the body of the bed-bug. The results of Howard and Clark may therefore assume an enlarged significance.

If infantile paralysis is transmitted in nature largely or mainly through the agency of the stable fly, this fact would render the suppression of the disease comparatively easy, whereas if the infection is spread largely from person to person through the intervention of carriers and missed cases the difficulties of the problem will be multiplied many fold. In the case of cerebrospinal fever it has been shown that carriers are ten times as numerous as the cases; if the conditions are analogous in infantile paralysis, the suppres-

sion of the disease will probably have to wait on specific therapy, of either preventive or curative nature.

The health officer impatiently asks: "Is poliomyelitis a contagious disease?" "Is it an insect-borne disease?" "Is it dust borne?" "Is it contracted from lower animals?" "Is it an alimentary infection?" or "Is it possibly, like typhoid fever, spread by several or all of these various methods of conveyance?" In the present state of our knowledge a definite answer cannot be made to these important queries, and we must await further work before the health officer can direct his measures to combat infantile paralysis with any assurance of success. Meanwhile the public must be given the benefit of the doubt, and the infection fought along all probable lines.

DISCUSSION

Dr. Simon Flexner: The statements just made by Dr. Rosenau are too precious not to be carefully regarded by us all, and the ideas expressed by him need to be widely disseminated. In the interest of Dr. Rosenau's investigations upon the possible conveyance of this disease by insect carriers, it is important that physicians everywhere should submit to him all the information possible.

THE PROBLEM OF TYPHUS FEVER IN THE UNITED STATES

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In a paper presented before this Association in 1911, Dr. Morris Lewis reported a study of 13 cases of "so-called Brill's disease" observed by him in the Pennsylvania Hospital. He stated that he was not convinced that the disease was not an atypical typhus fever, but that it remained for the laboratory worker to definitely settle the question.

Not long after Lewis' paper was published the identity of the disease, described by Brill and referred to by Lewis, with typhus fever was definitely determined by the work of Anderson and Goldberger. These workers found that the monkey was susceptible to infection with blood from cases of Brill's disease; and, by a series of cross-immunity tests, showed that monkeys that had recovered from Brill's disease could not be infected with Mexican typhus fever and, conversely, that monkeys resistant to Mexican typhus could not be infected with Brill's disease. This reciprocal immunity showed conclusively that the New York (Brill's) disease and Mexican typhus were identical.

Attention was first called to this symptom-complex by the papers of Dr. Nathan E. Brill, of New York, in which he clearly set forth the distinction between the disease described by him and typhoid fever. In the three papers by Brill he reports having observed in New York 254 cases of the disease from 1896 to 1910. Louria reported having observed 18 cases in the Jewish Hospital of Brooklyn during the summer and fall of 1910. Ziegal reported 3 cases in 1909

and 1910 from Beth Israel Hospital, New York. Roger Lee, from a study of the medical records of the Massachusetts General Hospital for the ten years from October 1, 1902, to October 1, 1912, concluded that typhus fever in a mild form had been present during that time in Boston and vicinity. He found in his study of the hospital statistics records of 28 cases which corresponded fairly closely to Brill's description of typhus.

Strouse, in 1912, reported the observation of cases in the Michael Reese Hospital, Chicago. Paullin reported, at the Southern Medical Association in 1912, having seen 7 cases in Atlanta since 1910. Cases have also been reported by Patek from Milwaukee, by Warren Coleman, of New York; and by Nicoll, Krumwiede, Pratt, and Bullowa from the Har Moriah Hospital, New York; by Charles, from Indiana; and by Goldberger, from Virginia.

From this it is quite evident that the prediction made by Anderson and Goldberger early in 1912 that typhus fever is actually present at all times in certain large cities of the United States has been verified and that the disease is even more widespread than they predicted. Roger Lee, in his studies of the 1404 cases of continued fever of a greater duration than seven days in the Massachusetts General Hospital from October 1, 1902, to October 1, 1912, found a ratio of about 1 case of typhus fever to 47 of typhoid.

There is reason to believe that this same ratio would hold, not only for all the cases of typhoid fever in Boston, but also for typhoid fever in certain other large cities of the United States. According to the *Public Health Reports for* 1912, published by the Public Health Service, the following number of cases of typhoid fever were reported in certain large cities of the United States during the year 1912:

	Cases.
New York City	3386
Baltimore	1067
Boston	477
Chicago	1039
Philadelphia	1620
Washington	607

If we assume that the ratio of 1 case of typhus to 47 of typhoid, found by Lee in the Massachusetts General Hospital, holds for

these cities, we may estimate that during 1912 typhus fever was present as follows:

	Cases.
New York City	72
Baltimore	22
Boston	10
Chicago	22
Philadelphia	34
Washington	12

That this is not an altogether unwarranted assumption is evident from the fact that, according to reports from two hospitals in New York City—Mount Sinai and the Jewish Hospital of Brooklyn—cases of Brill's disease or typhus and of typhoid fever were treated in those hospitals as follows:

	Year.	Typhus.	Typhoid.
Mount Sinai	1910	37	
Mount Sinai	1911	27	
Mount Sinai	1912	36	
Jewish Hospital	1910	22	45
Jewish Hospital	1911	10	46
Jewish Hospital	1912	19	44

From the above tables it is seen that the ratio of typhus fever to typhoid fever in the Jewish Hospital of Brooklyn for the three years 1910, 1911, and 1912 was 1 to 2.6 instead of the ratio of 1 to 47 as found by Lee in Boston.

The number of cases of typhoid fever reported to the city department of health of New York for the year 1910 was 3735. If we estimate the probable number of cases of typhus in the city that year by Lee's figures, we find the number to be 77. Now we find that for 1910 there actually occurred in two hospitals in New York City, 59 cases of typhus, leaving only 21 more cases to be accounted for in all the other hospitals and in private practice. In view of this, it is certainly reasonable to assume that there were fully as many cases unrecognized as were recognized and that the estimated number of 77 does by no means cover the number of cases of typhus that actually occurred in the city.

My only excuse for bringing this brief note to your attention is the hope that the subject may be kept before you so that cases which may come under your observation may be reported and more accurate data collected as to the prevalence of typhus fever in the

United States. While the disease, as generally observed, has had a low case mortality and shows but little tendency to spread, it is nevertheless apparently always present in our larger cities and the possibility should ever be borne in mind that it may acquire virulence and epidemic prevalence. The fact that over 321 cases of the disease have come under the observation of one physician justifies the assumption that perhaps cases may have passed unrecognized by others and that the disease exists in other localities than those from which it has been reported.

Guinea-pigs are quite susceptible to typhus fever when inoculated intraperitoneally with blood from cases of the disease during the active febrile period; the only indication in the animal of infection being the temperature curve which, in its rise, duration, and fall, is quite typical and readily recognized. I would like to suggest the inoculation of guinea-pigs with about 3 c.c. intraperitoneally of blood from cases of continued fever giving a negative Widal and blood culture as a procedure of value in arriving at a correct diagnosis, especially in cases where there has been a sudden onset, an atypical eruption, intense headache, apathy, and prostration. I think that it will be found that typhus fever is more frequently encountered, at least in our larger cities, than has been the previous quite general belief.

I am under obligations to Dr. Nathan E. Brill, of the Mount Sinai Hospital, and Dr. C. Eugene Strasser, Superintendent of the Jewish Hospital of Brooklyn, for statistics on typhus and typhoid fever in those institutions.

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DISCUSSION

Dr. W. H. Thompson: In 1859 and 1860 I was physician to the New York Quarantine Hospital, and in that service I was constantly seeing typhus fever among immigrants coming into that port. The typhus fever I saw at that time was as different from Brill's disease as smallpox is from measles. That disease was particularly contagious, and I had several friends who contracted the disease and died of it. I think it is very unfortunate to attempt to identify Brill's disease with typhus fever.

Dr. W. H. Park: We had the interesting experience of finding a family consisting of the father and three children; the father had the

symptoms of typical typhus, the children those of Brill's disease. Guinea-pigs and monkeys showed the usual reactions for typhus when inoculated from all these patients.

Dr. Lewis A. Conner: What are we to do with these cases? Shall they be reported as typhus fever or as Brill's disease?

Dr. Herman M. Biggs: There is no question but that these cases should be reported as typhus fever. Some uncertainty formerly prevailed in New York as to this question, because the diagnosticians of the Health Department had not been educated to recognize Brill's disease as typhus fever.

Dr. Anderson: With regard to the different types of typhus to be encountered, we saw many different types in Mexico. At the Mexico General Hospital the mortality rate was 5 per cent., and only the worst cases come to the hospital. We have seen cases of typhus fever of all grades and we have no doubt that Brill's disease is true typhus.

THE POSSIBLE RELATIONSHIP OF ORGANIC DISEASES OF THE NERVOUS SYSTEM TO RIGG'S DISEASE

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The occurrence of purulent disease of the alveolar processes is so common and so widespread that it has come to be regarded, unfortunately, only as disagreeable and esthetically offensive, but not dangerous and capable of causing serious disease. I have had some experience which convinces me that Rigg's disease may be the source from which serious organic diseases of the nervous system flow. Although I can offer you no other proof of the truth of this statement save the occurrence of such disease in persons afflicted with alveolar pyorrhea, the absence of any other etiology and the amelioration or disappearance of the disorder after the pyorrhea has been treated locally and constitutionally by means of autogenous vaccine, I am constrained nevertheless to present a few of these observations, briefly, for your consideration. From a large number of cases in which I believe Rigg's disease played the chief role in the causation of the nervous disease, I have selected three. In these the peripheral motor neurons were affected.

The first case that I shall cite was one of universal myokymia. Myokymia is the name given to a disease of unknown origin whose chief clinical manifestation is the occurrence of muscle waves and general weakness. It was first described by Kny (*Archiv f. Psych.*, vol. xix) and by Schultze (*Zeits. f. Neurol.*, vol. vi). Its occurrence has been attributed to exhaustion, to exposure to cold, to trauma and to lead-poisoning, but none of these have been proved to be causative of the disorder. That it is a rare condition is shown by the fact that I have encountered but five instances of it in the

examination of 10,000 patients. The course of the disease is extremely chronic, and in the absence of any cause which can be removed or overcome, the treatment is most unsatisfactory.

The patient, a merchant, aged forty-one years, married, of good habits, habituated to cricket, golf, and tennis, noticed in June, 1912, that his legs got tired and his gait feeble after comparatively slight effort, such as playing a round of golf or a set of tennis. These symptoms continued to increase rapidly and a month later he noticed that while playing cricket he could not focus properly, the ball would hit him instead of the bat. In the four months that intervened between the occurrence of these symptoms and the date when I first saw him, the easily induced fatigue, insecurity of station and gait, and the sensation of trembling in the muscles had increased to such an extent that he became nearly incapacitated for any work or pastime that required standing or walking. For instance, the day he came to see me he had to be assisted from the automobile into my house. The most conspicuous symptoms on physical examination were:

1. Constant wave-like movement in practically all the muscles of the body and of the limbs.
2. Abnormal liveliness of all the tendon-jerks, including an exhaustible ankle clonus but no Babinski or Oppenheim phenomena.
3. Nystagmus when the eye-balls were in forced lateral position and paresis of the right external rectus muscle.
4. Hyperidrosis.
5. Increase of electrical excitability of the muscles of the extremities.
6. Tremor of the outstretched fingers and slight transient tremor of the lips.

The myotatic irritability, however, was the striking symptom. As the patient lay quietly in bed the muscle waves could be seen extending from one end of his body to the other; short waves, one following another, in what seemed to be indolent succession. The most careful laboratory examination of his blood, spinal fluid, urine, gastric contents and feces showed no departure from normal. During the week that these examinations and observations were being made the patient was kept in bed, and at the end of that time myokymia was much less striking and the patient said he felt quite well. He returned to his business, but in a few days he returned with complaint of his infirmity. It was then that the suspicion crossed my mind that an obvious and severe pyorrhea which he had might have some relation to the disease. A culture was made from pus about the gum of the wisdom tooth and this culture revealed Gram positive coccus in short chains and pairs; Gram negative coccus, unidentified, few. Vaccine-streptococcus viridans, strength 1 c.c., 500,000,000. First dose was 0.1 c.c., 50,000,000, and an injection was given twice a week and increased by 0.1 c.c. or 50,000,000. January 24, 1913. Vaccine-

streptococcus viridans, strength 1 c.c., 1,000,000,000. First dose 0.1 c.c., 100,000,000, a reduction from the last dose of 500,000,000. The injections were given twice a week, increased by 0.1 c.c., 100,000,000, up to 0.5 c.c., or 500,000,000, thereafter once a week up to 1,000,000,000.

Meanwhile he was sent to a dentist for local treatment. Two months after the treatment had been instituted he felt well, the muscle waves and weakness of the legs no longer annoyed him and he went daily to his business. He was not seen then until March 18, 1913, when a call came from his place of business, saying that he had been suddenly taken seriously ill. When one of my assistants reached him he was told that the patient had been in excellent health up till the morning of that day. The day before he had walked two miles because he felt like walking and he was well enough to play a game of cricket. On the morning of March 18, he noticed at 11 o'clock that his feet were heavy. Gradually his legs and thighs became heavier and by three o'clock he found locomotion without support impossible. During this period he felt chilly and ill. At 3 o'clock he had several uncontrollable outbursts of sobbing without experiencing any subjective emotion, sobbing which seemed to the observer quite similar to that which is seen in patients who have thalamic disease. He was at once brought into the hospital and the physical signs, in addition to those which he had six months before, were elevation of temperature to 101° F., pulse 100, and inability to stand and walk unaided. Again the laboratory investigation threw no light on this inexplicable accession of symptoms. He had had the last injection of vaccine on March 16, 1913. A dentist was requested to remove two front teeth and from the cavity of one of them pus oozed.

On March 20, the following day, temperature was normal, he had slept well and was feeling much better.

On March 21, the patient was up and walking around the room, shaved himself, and was able to stand on either leg without aid. No headache following lumbar puncture.

On March 22, patient maintains that he feels quite well. The direct myotatic irritability of the muscles is much less than three days before. Tendon-jerks still active, no evidence of any myokymia. From that day to this the patient has gone to his business daily. There is no evidence of muscular weakness or myokymia and he seems to be well.

He who will not believe there must be a definite relationship between the pyorrhœa alveolaris and this most enigmatic symptom complex to which the name myokymia is given must be skeptical indeed.

The second case that I shall relate is a very complicated one, and to accept the statement that all his ill health was dependent upon disease of the buccal cavity will tax your credulity.

The gentleman afflicted, now aged fifty-eight years, had been singularly free from illness until his fiftieth year. Then after months of most strenuous devotion to and successful effort in an international sporting event, he was stricken with a disease which was at first supposed to be a polyneuritis, but which was found eventually to be a chronic parenchymatous myositis. After a week of malaise the patient complained of heaviness in all his extremities. Pain in the muscles of the extremities and of the trunk increased by active or passive movements and gradually he became paralyzed and helpless, practically unable to move a limb. There was no swelling of the joints, no tenderness over nerve trunks, but the swelling of the muscles in the shoulder and upper arm and the thigh could be readily made out. None of the ordinary attributable causes of poliomyositis, acute infection or intoxication of any kind could be determined, nor did the blood reveal evidences of eosinophilia. In the absence of any attributable cause it was thought it must be a manifestation of the gouty diathesis. The individual never had gout nor did his arteries or kidneys show any evidence of it. At the end of a year, during which time every resource, which a man of wealth could command, was concentrated on him, he gradually got well. The muscles that were the seat of the disease in its most advanced form underwent atrophy, evidently the interstitial sequela of the parenchymatous process, which after a long time was counteracted by exercise.

He remained well for three years, then without attribution of any kind he complained of malaise, headache, lack of energy and general depression. The upper lobe of his left lung revealed a general tuberculous infiltration. Two months later he had his first hemorrhage which was followed by most profound prostration and mental depression, and both the physical examination and *x*-ray revealed the extensiveness of the tuberculous process. Bacilli were never very numerous in his sputum. He lost about twenty-six pounds in weight, had fever for upward of two months, but at the end of the year he was apparently well. Again he remained well for about three years.

One evening in September, 1912, after he had returned from the races in Paris where he had subjected himself to some emotional strain, he complained of a strange fluttering in his chest, a sensation of uneasiness, and state of apprehension without cause. At the end of a week's observation the Parisian physicians made the diagnosis of cardiac fibrillation, and put him on a course of treatment including digalen. At the end of a month he came home. The fibrillation which he had on his return was depicted by electrocardiograms, which were absolutely typical. He had a profound attack of prostration. He was kept in bed five weeks, during which time the most benefit was obtained from the administration of digipuratum, but the evidence of the fibrillation remained conspicuous.

Physical examination of the heart revealed no valvular or detectable muscular disease. It was assumed, however, that the fibrillation of the auricles must have been the direct outcome of a chronic myocarditis probably the result of a coronary arteriosclerosis, though no evidence of arteriosclerosis could be found in any part of the body. Save for a diminution of the hydrochloric acid in the gastric juice all laboratory examinations were negative.

He was kept in bed for four weeks and given digalen; later digipuratum was substituted. He felt some improvement, but not much. The deficit, however, disappeared. His symptoms were profoundly neurasthenic. Every second day he complained of stiffness of the joints, of the hands, and elbows, occasionally of the knees and unattributable malaise, headache, and depression. On inquiry he reported that he found blood occasionally on his tooth brush. Examination revealed an extremely mild pyorrhea, from which a culture was made.

December 17, 1912. Vaccine-streptococcus viridans, strength 1 c.c., 500,000,000. First dose was 0.1 c.c., 50,000,000, and an injection was given twice a week and increased by 0.1 c.c. or 50,000,000.

January 24, 1913. Vaccine-streptococcus viridans, strength 1 c.c., 1,000,000,000. First dose 0.1 c.c., 100,000,000, a reduction from the last dose of 500,000,000. The injections were given twice a week, increased by 0.1 c.c., 100,000,000, up to 0.5 c.c. or 500,000,000, thereafter once a week up to 1,000,000,000.

February 26, 1913. Vaccine-streptococcus viridans, strength 1 c.c., 1,625,000,000. First dose 0.5 c.c., 812,000,000, a reduction from the last dose of 1,000,000,000. Injections were given once a week and increased by 0.1 c.c., 162,000,000, for five doses and followed by three doses of 1 c.c., 1,625,000,000, once a week.

From the time when the evidences of the local disorder disappeared under topical treatment and he had received ten vaccinations, the patient began to get well. Now he rides, walks, plays golf in moderation, and comports himself like a normal man.

An electrocardiogram made a few days ago by Dr. W. B. James shows the fibrillation of the auricle still in existence. What relation the disease which this individual has had to Rigg's disease is I do not know; but the message that I tell is that he seems to have got better after the Rigg's disease had been overcome.

The third case that I shall relate as an example of organic disease of the nervous system following in the wake of a condition caused by purulent gingivitis is one of multiple neuritis, which made unimpeded progress to death.

The patient, a farmer, aged sixty years, complained of pain and soreness in the lower extremities, of a sensation of drawing, of tightness in the feet and legs, of enfeeblement in the lower extremities, of rapid fatigue on exercise, and of general weakness. These symptoms he thought had come on two years before I saw him, that is, in the summer of 1909, but on inquiry he admitted that he had not been well for eight or ten years. It was as long ago as that when he noticed that he could not do as much work as he formerly could do, that he fatigued easily, and that he often had pain in the back. He thought this was due to a slight attack of rheumatism which he had twenty years ago. Three years before coming under observation he had several attacks of pain over the sternum, dull, heavy, deep pain, whose intensity increased for about an hour then gradually wore away. It had no relation to taking food nor was it affected by antirheumatic medicines.

In May, 1911, he complained of a sensation of constriction in the bottom of feet and toes and of increased sensitiveness of the toes. When he moved the toes they would feel like a rubber ball. During the summer, weakness of the feet and legs developed, and he was unable to go to his farm. In the early autumn he first noticed that he could not clear the toes in walking, and this increased until complete foot-drop developed. The next symptom aside from sexual impotency, which was an early symptom, was atrophy of the lower extremities and general emaciation.

When I saw him early in 1912, he had the typical objective symptoms of multiple neuritis, *i. e.*, tenderness over the nerve trunks, symmetrical muscular atrophy, loss of the tendon jerks, degeneration in the affected nerves and muscles, and objective sensory disturbance non-segmental in distribution, hyperesthetic in some areas, hypoesthetic in others.

Examination of the blood on various occasions showed a mild degree of secondary anemia, and with considerable number of leukocytes, but with no increase in the number of lymphocytes. For instance, on January 1, 1912, the blood showed: Hemoglobin, 89 per cent.; red-blood corpuscles, 4,882,000; white-blood corpuscles, 19,000; differential count. Neutrophiles, 76 per cent.; eosinophiles, 1 per cent.; basophiles, none; large lymphocytes, 7; small lymphocytes, 12; mononuclears, none; transitional, 4 per cent. The red-blood corpuscles showed a mild polychromatophilia.

The cerebrospinal analysis showed a negative Wassermann; positive globulin content, no cells and reduced Fehling's solution. The serum Wassermann was negative.

Analysis of the stomach contents showed a decided subacidity; total $\frac{10}{40}$, no free hydrochloric acid, normal pepsin content and no lactic acid. Gross, chemical, and microscopic examination of the stools showed no abnormality. The same was true of the urine save that there was constantly an excess of indican and occasionally a trace of urobilinogen. The pulse and temperature chart shows that each day there was an elevation

of temperature in the afternoon, always as high as 100° mouth temperature, and here and there 100.5° to 101°. The morning temperature was approximately normal. The pulse kept pace with the temperature. In the morning it averaged from 78 to 85, in the afternoon 90 to 100.

The slight febrile state and the blood-picture were the only suggestions of a possible infectious origin of his disease, but the source of this infection was a profound purulent gingivitis which was not suspected until he was seen again. During several weeks he was subjected to general restorative treatment: massage, electricity, packs, injections of strychnine, etc. He made no progress under such treatment, and a dentist was then called. Many pus pockets were opened and surgical treatment of the disease begun. No cultures unfortunately were made. The patient could not be persuaded that this had anything to do with his total incapacity, and he insisted upon going home, where he died six months later, the disease, it is reported by his physician, having made steady progress.

DISCUSSION

Dr. W. W. Ford: How soon did the improvement begin in Dr. Collins' patients after the beginning of vaccine therapy? In observing some cases treated with vaccines in Baltimore, the improvement of symptoms seemed to follow too quickly to beget confidence.

Dr. Collins: In my cases no improvement was noticed for several weeks after the vaccine was started.

Dr. Frank Billings: I not only agree with Dr. Collins as to the possibilities which may arise from a chronic septic focus, but I would go a step farther and say that not only may the neuromuscular system be affected, but there may be produced degenerations of the myocardium, etc. And there may be more conditions able to give rise to these remote disorders than Rigg's disease, *e. g.*, alveolar abscesses, infected tooth pulps, infected faucial tonsils, infected sinuses, infected gall-bladders, etc. The present widespread use of vaccines is a furore which will wane; we need to attack directly and remove the source of infection; body-immunity will then come up without the stimulus of vaccines. Vaccines without proper hygiene may fail; probably will fail always in the long run.

Dr. Frederick T. Lord: I should like to confirm Dr. Billings' remarks as to the possibility of hidden infection in and about the teeth; and in that connection, I wish to call attention to the value of *x*-ray photo-

graphs of the maxillary region in disclosing the presence and location of such infected foci.

Dr. Chas. S. Bond: I wish to report two cases of epilepsy occurring in young men, both having seizures every day. After the discovery and cure of alveolar abscesses, there has not been a single seizure in the case of one of these patients, and but one seizure in the case of the other.

Dr. Lewis A. Conner: What are we to do if we take *x*-ray pictures of all our patient's teeth? I predict that we will find abscesses somewhere about the teeth of the majority; shall we then sacrifice all these teeth? It must be a curious organism that is able to produce any train of symptoms from epilepsy to auricular fibrillation. I readily concede the importance of oral sepsis as a source of danger to the human organism, but I certainly deprecate this tendency to accept it as the ultimate cause of such various and serious manifestations of disease.

Dr. Collins: Dr. Conner should not be apprehensive for his patients' teeth, even if abscesses be found; it is only necessary to employ the right dentists, who do not remove such teeth. In view of Dr. Conner's remarks, I am sorry that my second case had auricular fibrillation, but he did have it and his symptoms all improved with the improvement of his Rigg's disease. I was interested in Dr. Bond's cases, and in that connection, I might cite a case seen with Dr. Taylor in which a streptococcus viridans infection had caused a local meningitis with epileptiform seizures; of course this was not true epilepsy. It is important to establish centres in large cities for the treatment of Rigg's disease, and dental infirmaries should be utilized for this purpose. I agree with Dr. Billings that in all cases suffering from chronic foci of infection that the greatest care in hygienic management is necessary. Vaccine therapy is far from the whole thing in treatment.

IS SERUM ANAPHYLAXIS A DANGER OF SUFFICIENT IMPORTANCE TO LIMIT OUR USE OF PROTECTIVE SERA IN THE TREAMENT OR PREVENTION OF DISEASE

By WILLIAM H. PARK, M.D.
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The antitoxin treatment of diphtheria soon brought to light that the injection of the proteins of a foreign serum, such as that obtained from the horse, into man was sometimes followed by certain disagreeable and even dangerous effects. These, after a first injection, usually became manifest after a number of days. The name of serum sickness has been applied to the reaction since the classical work upon this subject in 1905 of von Pirquet and Shick.

The usual reaction is not of serious importance except in young, very sick children in whom the rise of temperature, urticaria, etc., may somewhat lower the resistance and predispose the patients to complications. In a few cases the symptoms are more pronounced, albuminuria, joint complications, swelling of mucous membranes, and intense scarlatiniform rashes being added. These disagreeable results are nearly as marked after a first injection as following later ones. They are apt, however, after a later injection, when sensitization has taken place, to come on after a shorter lapse of time. The heating used and the elimination of much of the serum proteins in the refining of the antitoxins have largely eliminated the more severe types of this common form of serum sickness in cases of diphtheria and tetanus treated, but the other immune sera are not, as a rule, refined and their injection is still accompanied by the usual percentage of severe serum reactions.

The object of this paper is not to consider in detail this usual form of serum sickness, but the occasional cases of collapse in which death may occur within a few minutes after the injection of serum. While these cases are classed with those of serum sickness their pathology is not fully understood. They occur as often after a primary injection as after later ones. Death probably takes place only when the anaphylactic shock occurs in an abnormal individual, such as one suffering from the condition of status lymphaticus or subject to asthma.

H. F. Gillette, interested in these cases through a personal experience, made an investigation and was able to collect 28 cases, of which 15 died. Later, Rosenau and Anderson collected 19 cases. There are undoubtedly a number of cases besides these which have occurred, but have not been recorded.

The reason for these sudden deaths has received various explanations. The symptoms are in many respects like those of anaphylaxis, pricking sensations frequently occur first, then spasms and failure of respiration while the heart continues to beat. The frequent history of previous asthmatic attacks led Schultz and Jordan to suggest the abnormal development of the smooth muscle of the bronchi as an explanation of the symptoms in these cases, while the work of Rosenau and Amoss indicate the possibility of sensitization to horse serums through inhalation of protein material exhaled by horses. The deaths, when they occur, are so sudden and unexpected that they make a great impression upon those who witness them and also upon those who read or hear of them. This is so strong that many advise that immunization against diphtheria be stopped so as to eliminate danger if a serum injection is needed in future years. As a matter of fact, these fatal cases are extremely rare.

The experience of physicians in the employ of the New York Department of Health with the use of serum in the hospitals and among the poor is of the utmost value in estimating the frequency of these reactions. All cases of diphtheria treated in the Department Hospitals since January 1, 1895, have received diphtheria antitoxin either in the whole serum or in solution of globulins. During this time there have been over 30,000 patients treated without a single

death due to anaphylaxis and with only 2 cases of severe collapse. Both these recovered completely.

During the past five years all cases of scarlet fever admitted to the hospitals have received an immunizing dose of antitoxic globulins. Over 16,000 have received whole serum or globulin solution and very many a second injection after the proper period for sensitization, and not a single case of collapse has occurred.

In the city since 1895, the inspectors have given treatment or immunizing doses to about 105,000 persons. Two deaths followed the injections. In one of these an autopsy was obtained and a marked case of status lymphaticus was found. The records of the inspectors give no information as to cases of collapse followed by recovery. Private physicians have reported to me 3 cases of deaths and 2 of collapse. How many others have occurred in private practice and what the proportion is to all cases treated, I have no means of estimating. It is because of knowing the total cases treated as well as the total fatal accidents that the extensive records of the Health Department are so valuable.

It is very important to note that every death followed a primary injection. It is realized that the number of primary injections far exceeded later ones. There was one case of temporary collapse during a second injection, but in this case the second dose was given intravenously. A study of these figures clearly proves that the cases of collapse and death after subcutaneous or intramuscular injections of antitoxin are so rare that they should never prevent the use of serum where it is really indicated and that the fear of sensitizing a patient is practically groundless. Intravenous or intraspinal injections are more apt to be followed by serious symptoms, but these can be largely avoided when the serum is given properly.

It is true that most of these cases will have within twenty-four hours a slight rise of temperature, and if a rash develops it is apt to occur early rather than late; but unless one watches the cases closely it is unlikely that the observer would suspect whether the cases received a primary or a repeated injection. In order to test the results following a second injection, a number of patients

which had each received some weeks before an injection of 1 c.c. of serum were given varying amounts with the following results:

Reaction following Injection of Sensitized Persons

No.	Amount of second injection. units.	c.c.	Number having temperature rise.	Rash.	No. reaction.
15	10,000	10	6	10 (urticaria)	5
9	5,000	5	5	2 (urticaria)	4
9	1,000	1	3	1 (urticaria)	5
4	500	½	3	0	1

They were all given at a time when the patients were highly sensitized. Twenty-six of the persons received the serum between the thirtieth and seventieth day after the first injection. The urticaria was mild in all and none of the children appeared sick. It appeared in from two to eighteen hours. The rise of temperature was in most less than 2° F., but in three it was from 2.5° to 3.5° F. The number of slight reactions (fifteen in thirty-seven) is high, but many of those were so slight that they would have been overlooked except for the unusually close observation given them.

Others report similar experiences. Goodall states that in 63 cases given a second injection between thirty-five and three hundred and sixty-five days, there were 3 severe and 14 moderate reactions. There were no cases of collapse. Nemmser[1] studied histories of 900 receiving a second injection and 102 three or more injections. None of these 1002 cases suffered from collapse or died.

Intravenous Injections. The number of patients who receive serum intravenously is but a small fraction of those who receive it subcutaneously. My own experience is largely limited to about 300 cases receiving 5 to 7 c.c. of antitoxic globulins treated at the Willard Parker Hospital. Among these there have been no serious symptoms in primary injections, or in quickly repeated injections. A moderate number of cases of scarlet fever have received large injections of 100 to 200 c.c. of antistreptococcus serum two to twenty days after an immunizing injection of diphtheria antitoxin. One case of serious collapse happened. This was in a child suffering from scarlet fever, who three weeks previously had received a

[1] Deutsch. med. Woch., 1913, No. 16, p. 740.

protective inoculation of diphtheria antitoxin. Not infrequently a slight chill followed the intravenous injection. The serum or globulin solution should be warmed to a little above the body heat, and injected slowly.

Intraspinal Injections. The intraspinal injections have given the greatest percentage of accidents. Most of these are believed to be from too rapid changes in the intraspinal pressure rather than to anaphylactic shock. Drs. Sophian and Du Bois, who have in their work for the Health Department during the past few years injected many hundreds of cases, rarely have a collapse, and have had no death immediately following the injection, while some with less experience have had many cases of collapse and some deaths. The serum should always be injected slowly and the condition of the patient carefully watched. The injection should rarely exceed the amount of the spinal fluid withdrawn and should be immediately stopped when any untoward symptoms develop. The intervals between the injections are usually too short for the development of anaphylaxis.

Tests Used to Disclose Dangerous Liability to Anaphylaxis. Moss in 1910 drew attention to the value of the intracutaneous test to discover persons liable to shock. He found that 5 of 21 persons who had previously received serum injections responded within a few hours with a local reaction. With the assistance of Dr. Wood, I tested a number of injected cases after the lapse of two or three weeks and found that they regularly developed an immediate reaction in the skin of the point of intracutaneous injection. When given the second serum injection, nearly 50 per cent. showed, within a few hours, either fever or urticaria, but none of the reactions were severe. Dr. Wood gave an intracutaneous test to fifty consecutive patients on their admission to the hospital for diphtheria. Three of these showed an immediate reaction. Each then received 10,000 units. All three developed urticarial rashes and a rise of temperature within twelve hours, but in none were the symptoms in the least alarming. I think it would be a mistake to be influenced by his test except in cases in which a history of *asthma* was present. Here an absence of reaction would lead us to use the antitoxin more freely.

Preventive Measures. A number of investigators have shown that large doses of chloral, atropin, or ether will prevent the development of shock. The doses to be effective must be very large and would probably be more dangerous than the peril they were used to obviate. Dividing the dose into several portions seems to be the best available practical measure. The first subcutaneous injection should be not over ½ c.c. The cases of sudden death have happened as frequently after 2 c.c. as after larger doses. If no reaction, local or general, occurs within one hour, a second injection of ½ c.c. can be given and if this is well borne, repeated doses of the same size at hour intervals are probably safe. In a number of animal experiments I have found it safe to inject sensitized guinea-pigs with properly divided doses.

DISCUSSION

Dr. Simon Flexner: I should like to say a word about accidents following the intraspinal injections of antimeningitis serum. It goes without saying that such accidents are more apt to occur in anaphylactic persons when sera are given intraspinally than when given subcutaneously. The number of such accidents has not been large, but the figures have not been accurately assembled. It is obvious, of course, that extraordinary care is needed in making intraspinal injections; and at the Rockefeller Institute the importance of making simultaneous estimations of the blood pressure has been demonstrated.

It has been suggested, especially in the lay press, that the phenol or other preservatives present in sera may be the cause of accidents. It is difficult to say absolutely that such a thing may not happen, but it seems hardly likely in view of the extremely small dose of phenol contained in sera; and, moreover, the same sort of accidents are reported from France, where no preservative is used in sera. Three possibilities suggest themselves as to the cause of these accidents: (1) Anaphylactic shock; (2) pressure; and (3) preservatives in the serum. It seems to me that the third ought to be put last and disregarded in the practical use of sera.

Dr. Frank Billings: We have recently had some instructive, though alarming, experience with a polyvalent antistreptococcus serum, made by immunizing horses with streptococci obtained from numerous infected foci. We used this serum on twenty-five patients for immunizing pur-

poses, and more than one dose was necessary. Although care was taken in the use of this serum, anaphylactic phenomena were observed in a number of cases after the third or fourth injection, usually rather mild in character; but three patients nearly died in collapse after the injection of 10 c.c. of refined serum. We managed to save these patients by the use of atropine sulphate and adrenalin chloride, which we had ready at hand. Our experience in these cases led us to abandon the use of the serum. The three serious accidents happened, one after the fifth, one after the third, and one after the second injection.

Dr. C. F. Withington: I recently encountered an instance of severe anaphylaxis in the son of a Boston oculist. This patient at the age of three years had had conjunctival diphtheria; at the age of eighteen he had laryngeal diphtheria, and his breathing became much embarrassed. It was necessary, of course, to give antitoxin; although the danger of anaphylaxis was considered, the young man's father recalling the early history.

The first dose of five thousand units was well borne, but, the symptoms not abating, after twenty-four hours twenty thousand units more were given, followed by very grave symptoms of anaphylactic shock. Fortunately the patient recovered.

Dr. S. J. Meltzer: I listened yesterday to Dr. Weil's analysis of Besredka's method to prevent anaphylaxis; we are entirely helpless against such accidents. Their rarity in earlier days was due partly to good fortune and partly to the almost exclusive use of subcutaneous injections.

As Auer has shown that the use of atropin will greatly reduce the danger of anaphylactic shock, this drug should be given always when the possibility of anaphylaxis is suspected.

Dr. John F. Anderson: I feel, with Dr. Flexner, that the preservative present in sera has nothing to do with the production of serum accidents. Not more than 0.4 per cent. of trikresol may be used in sera, and animal experiments have shown that the toxic dose of this and like phenols is enormously greater than that present in any conceivable dose of serum.

Dr. J. J. Kinyoun: I have been studying anaphylaxis by attempting to desensitize animals. A horse was immunized by gradual, repeated injections until the blood became strongly hemolytic; transfusing this blood to another horse, the second horse's blood became strongly antitoxic. A small amount of the antitoxic blood, mixed with a toxic serum, preserved the lives of guinea-pigs, but unfortunately I found that the precipitins increased *pari passu* with the antitoxin.

Dr. Park: There can be no doubt that serum from certain horses is more dangerous than that from others. As in Dr. Billings' cases, someone must have the bad experiences. Even in Dr. Billings' series, however, only one had bad symptoms after the second injection.

It is possible to desensitize animals by following a small dose in two or three hours by a second injection.

I did not wish to underestimate the value of atropin and adrenalin in the treatment of anaphylactic shock; but Auer's work indicates that atropin must be given to the maximum dose to prevent the phenomenon, and is then not always sure to do so. I believe in view of the comparative safety of refined sera, and the rarity of accidents, it is better not to give such large doses of atropin to combat a condition which may not arise.

In the case of the Cincinnati accidents, the same serum had been used on other patients with no ill effects; it is likely, therefore, that here we are dealing with individual idiosyncrasies.

SPONTANEOUS RUPTURE OF THE SPLEEN IN TYPHOID FEVER; WITH REPORT OF A CASE CURED BY OPERATION

By LEWIS A. CONNER, M.D., and WILLIAM A. DOWNES, M.D.
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The spontaneous rupture of the spleen in the course of typhoid fever is sufficiently rare to warrant the report of a case; more especially as in this instance it was possible to make the diagnosis and, by prompt operation, to save the life of the patient. Only twelve other cases are recorded in the literature. In nine of these the condition was discovered at autopsy. In the three remaining cases it was found in the course of operation done for supposed intestinal perforation. None of these cases recovered.

A physician, aged thirty-six years, was admitted to the New York Hospital on February 20, 1913, with the diagnosis of probable typhoid fever. Up to the onset of his symptoms, seven days before, he had never been seriously ill in his life. He had never had malarial fever, nor any other disease likely to lead to enlargement of the spleen. At the onset the symptoms were those of a catarrhal cold, sore throat, and slight cough. With these were increasing fever, headache, general body pains, malaise, weakness, and troublesome nausea.

Physical Examination. Muscular, well-nourished body. High color and flushed face. Moist, slightly coated tongue. Throat somewhat congested. Chest well-developed. Lungs show everywhere normal resonance. Good, vesicular respiratory murmur. No adventitious sounds, except an occasional sonorous rhonchus. Heart normal in size and position. Apex-beat felt in fifth space, 8 cm. to left of midsternal line. Sounds clear and normal in character. Action regular and strong. Pulse large, full, and slightly rapid, palpable arteries normal. Abdomen full and soft. No rose spots. Liver dulness extends in mammillary line from sixth rib to free border. Liver edge not felt. Both kidneys indistinctly felt; not

tender. Area of splenic dulness is considerably increased and extends from eight to eleventh rib and anteriorly 3 cm. beyond the costal margin. The edge of the spleen is distinctly felt, even with quiet respiration. On deep inspiration it extends fully 4 cm. below the costal margin. It is unusually broad, its edge blunt and rounded, and its consistence noticeably firm and tense. Palpation of the spleen causes distinct tenderness. The extremities are normal. There is no enlargement of the superficial lymph nodes. Admission temperature, 100.4°; respirations, 22; pulse, 88.

February 21. The patient passed a restless night, with much headache and general discomfort, and these symptoms continued throughout most of the day. At 7.15 P.M. he complained of a sudden, sharp, stabbing pain in the left hypochondrium. This was soon followed by severe aching pain in the left shoulder, which radiated somewhat down the left arm. Soon after the onset of the pain he vomited a small quantity of clear fluid and broke into a profuse perspiration. The pain was so severe as to require an injection of morphine. The respirations were rapid and shallow; there was marked tenderness to pressure just below the costal margin, where the spleen could be distinctly felt, and slight rigidity of the upper part of the left rectus muscle. At times the pain was felt somewhat in the right hypochondrium.

February 22. The severe pain in the left side and left shoulder continued throughout the night in spite of a second injection of morphine. When seen in the morning the patient looked much more seriously ill. His eyes were sunken, his features drawn and anxious, his respirations shallow and hurried. There was still distinct tenderness in the left hypochondrium and slight muscular rigidity, so that the spleen could not be felt distinctly. The area of splenic dulness, however, seemed larger than on admission. Elsewhere, the abdomen was soft and showed no tenderness on palpation. At the base of the left chest posteriorly the respiratory murmur was feeble and a distinct friction-sound could be heard both on inspiration and expiration. The spontaneous pain had lessened but was aggravated by the slight, dry cough that was present. The ache in the left shoulder and left supraclavicular fossa persisted.

February 23. The patient passed a restless, uncomfortable night, complaining chiefly of headache and nausea. At times he was slightly delirious. During the day his general condition and appearance improved much and he was able to take and retain a fair amount of liquid food. The bowels were moved satisfactorily by enema. The pain in the left side had ceased to be troublesome, but there was still slight tenderness in the left upper quadrant. The physical signs in the chest were unchanged, and it was still impossible to determine the nature of the violent attack he had had two days before. The occurrence of a pulmonary infarct was suspected but neither the symptoms nor the physical signs were sufficiently

characteristic to justify that diagnosis. The extremities showed no indications of thrombophlebitis.

February 24. The patient's general condition had still further improved and he passed a comfortable day and night and seemed to be settling down to a fairly normal typhoid course. Although the Widal test was still negative, blood cultures taken on February 21 showed a Gram-negative bacillus which resembled the Bacillus typhosus, and which two days later was indentified positively as such.

On the morning of February 25, the patient awoke refreshed after a comfortable night. At 8.30 o'clock, however, he had an attack of coughing and immediately afterward complained of the same very severe pain in the left hypochondrium and left shoulder. This pain continued throughout the morning and was accompanied by profuse sweating and by the same startling change in appearance and general condition. When seen by one of us (Conner) about 11.30 A.M., he had, in even more marked degree, the sunken eyes, the pinched features and anxious look that had characterized his first attack. His pulse was rapid, small, and soft; his respirations rapid, his skin covered with cold sweat, and he complained of weakness and nausea. It was evident that something serious had happened, and that his condition was growing progressively and rapidly worse. Examination of the chest showed no change from that of the preceding days. Aside from some diminution of the respiratory murmur at the left base posteriorly and a few rales, the pulmonary signs were normal. There was dulness on percussion over the greater part of the left side of the abdomen and in the left flank and some rigidity and tenderness in the left upper quadrant. The rest of the abdomen was soft and flat, and while having a somewhat boggy feel, was not tender. The liver dulness was normal. Drs. William A. Downes and S. W. Lambert were called in consultation and it was agreed by all of us that the symptoms indicated a rupture of the spleen. This diagnosis was arrived at by considering the location of the pain, tenderness, and muscular rigidity, by the absence of signs pointing toward other likely complications such as intestinal perforation and pulmonary infarction, and finally by the fact that the spleen had been recognized as being unusually large and tense for the early days of typhoid fever. With the hope of obtaining some confirmatory evidence of severe hemorrhage, a blood examination was made some three and a half hours after the onset of the pain, and when the symptoms pointed strongly to an alarming loss of blood. The examination gave the following results: red cells, 5,280,000; hemoglobin (Sahli), 85 per cent.; leukocytes, 35,000.

In spite of these apparently inconsistent blood findings, an immediate exploratory operation was decided upon and at 1.45 P.M. (five and one-quarter hours after the onset of the symptoms) the patient was taken to the operating room. The temperature, which at 8 P.M. had been 102.8°, had fallen to 100°, the respirations were 32; the pulse-rate 118. Dr. Downes,

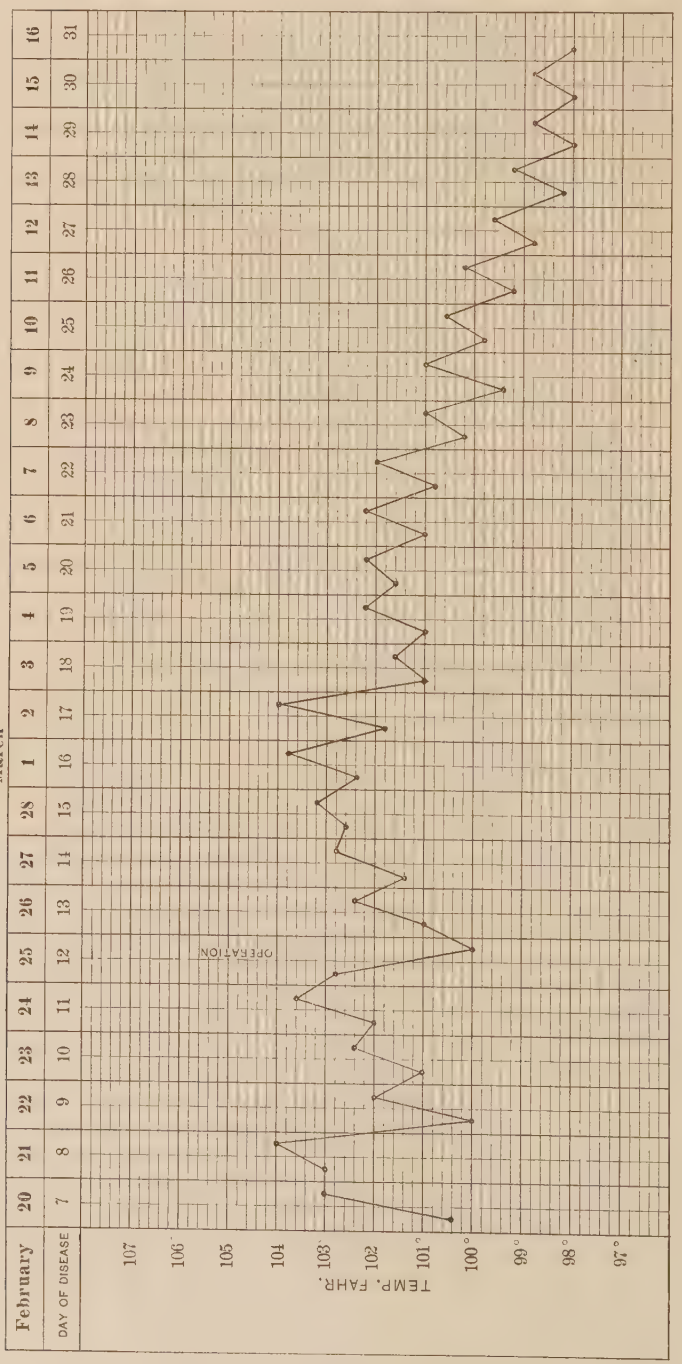

Chart of case of rupture of spleen during typhoid fever.

under local anesthesia, opened the abdomen by a vertical incision through the middle of the left rectus muscle. Upon entering the peritoneum the abdomen was seen to contain a great quantity of blood. The patient was therefore given nitrous oxide gas and ether (by Dr. Thos. L. Bennett), and the incision rapidly enlarged to an extent of eight inches. A tremendous quantity of fresh and clotted blood, estimated at from one and a half to two quarts, escaped from the abdomen. The left hand was passed immediately to the pedicle of the spleen, which was grasped between the index and middle fingers and the spleen delivered from the wound with the right hand. At this point the pedicle was caught with a long, straight, rubber-covered clamp placed close to the spleen. The vessels were then ligated, about two inches proximal to the clamp, with No. 2 chromicized catgut. The larger blood clots were rapidly removed; one old and laminated clot, fully an inch thick, conforming to the size and shape of the phrenic surface of the spleen, was found high up under the diaphragm. The abdomen was closed by layer sutures without drainage. Time of operation, twenty minutes.

When the hand was first passed behind the spleen, lying in its bed, a rent in the capsule, fully three inches in length, was encountered running along the posterior border, and during the manipulation this rent was so enlarged by the time the organ was brought out of the wound, that the capsule had been stripped from almost half its surface.

In spite of his critical condition on the operating table, which required an intravenous infusion of salt solution, the patient improved steadily during the succeeding twelve hours. His loss of fluid was replaced by saline solution given by hypodermoclysis and by the Murphy "drip." At 10 P.M. the hemoglobin percentage had fallen to 62 and his leukocytes numbered 68,000. On the following morning, (February 26) the pulse had fallen to below 100 and his general condition was very satisfactory. At 2 P.M. an examination of the blood gave the following results: red cells, 2,810,000; hemoglobin, 58 per cent.; leukocytes, 36,400.

On March 2 the patient complained of some pain in the left shoulder. There was no cough or other symptoms, but examination of the left chest posteriorly revealed an area of dulness over the middle portion of the lower lobe and, corresponding to this, a small area over which bronchial breathing and bronchophony could be heard. At that time the extremities showed no signs of thrombophlebitis.

March 3. Widal test positive.

March 5. Slight tenderness on pressure over lower part of left calf. The median basilic vein of the right arm was thrombosed at a point distal to the place of the infusion puncture at the time of the operation and showed as an indurated, tender cord 8 cm. long. The area of bronchial breathing in the left lower lobe had disappeared, but over the lower half of the lower lobe there was marked dulness, absence of breath sounds, and

fremitus and distant, nasal voice. There was slight cough and occasional pain in the left axilla, but no expectoration.

During the next few days the tenderness in the left calf became more pronounced and more extensive, and a similar area of tenderness appeared in the right calf, together with an indistinct elongated area of induration. These indications of thrombophlebitis gradually subsided, as did the signs of pulmonary infarction.

By March 15 the temperature had reached normal and the patient was convalescent.

On March 31 he was able to leave the hospital and one month later had regained his lost weight and seemed in almost his usual health.

TABLE OF BLOOD EXAMINATIONS

Date.	Red cells.	Hemoglobin, per cent.	Leukocytes.	Polymorph.	Lymph and Large mono, per cent.		
Feb. 20, 1913	....	..	8,800	71	17	11	
Feb. 22	....	..	13,400	60	30	10	
Feb. 25, 12 M.	5,280,000	85	35,000	87	13		
Feb. 25, 10 P.M.	....	62	68,000	91	9		
Feb. 26, 2 P.M.	2,800,000	58	36,400	86	14		Normoblasts
Feb. 28	....	..	24,800	67	22	10	Myelocytes and normoblasts
Mar. 1	....	58	30,000	83	17		Normoblasts
Mar. 12	....	62	15,800	82	17		
Mar. 23	....	71					

Pathological Report (Dr. Tytler). The spleen is of about normal shape, is swollen and firm, and measures 14 cm. in length by 11 cm. maximum width by 7 cm. maximum thickness. Weight, 375 grams. The anterior border shows one shallow notch near the anterior extremity. The capsule shows an extensive tear starting about the middle of the anterior border following that border to the posterior extremity, thence obliquely across the renal surface to the middle of the posterior border and thence along that border almost to the anterior extremity. The flap formed by this tear is loose and completely separated from the diaphragmatic surface. The capsule itself is thin, smooth, and transparent everywhere.

The separate mass of blood-clot received was removed from the diaphragmatic surface. It is disk-shaped and measures about 12 cm. in greatest diameter by 2 to 3 cm. in thickness. It is firm, dark-reddish brown, and shows a definite laminated structure on section.

The surface of the spleen over the area from which the capsule was separated is smooth, dark red in color, and shows no laceration or rupture. On section the spleen cuts readily, leaving a swollen, congested, slightly indurated cut surface in which the lymph follicles and trabeculæ can just be distinguished.

Microscopic sections show the spleen pulp much congested and packed with large phagocytic endothelial cells both in and between the sinuses. The endothelial lining of the sinuses is swollen and shows some proliferation. Small leukocytes are seen in the sinuses and between them. The pulp cords are compressed and the lymphocytes relatively fewer than natural. The lymph follicles are of about natural size and show no significant lesions. The whole picture corresponds to the usual findings in the spleen of typhoid fever.

The capsule in the section examined (from the hepatic surface) shows no abnormalities. It is of natural thickness and consists of mature fibrous tissue with no cellular infiltration.

Discussion. The reasons for the diagnosis of rupture of the spleen have been given. The condition probably would not have been recognized had it not been for the fact that attention had been directed to the spleen by reason of its unusually large size and firm consistence. When once the possibility of its rupture had been thought of, the symptoms seemed to correspond so perfectly with what might be expected under such circumstances that the diagnosis could be made without much hesitation.

Two further points of interest deserve mention. The discovery at operation of a layer of old, laminated clot lying directly over the dorsum of the spleen made it certain that the acute symptoms which appeared three days before the day of operation indicated the time of the first rupture of the splenic capsule. These symptoms had entirely subsided before the second attack of pain, which followed immediately upon an attack of coughing. At this time evidently there was either an increase in the rupture of the capsule or a displacement of the old clot and subsequent uncontrollable bleeding from the site of the old tear. The subsidence of the symptoms after the first attack of pain suggests the possibility that, rarely, a rupture of the capsule of the spleen may be followed by spontaneous cessation of the bleeding and recovery.

The second point of interest relates to the character of the blood, as shown by examination, at a time when all the symptoms indicated

an alarming internal hemorrhage. At that time the red cells numbered over 5,000,000 to the cubic millimeter and the hemoglobin percentage was 85. This apparent inconsistency was interpreted as meaning that the hemorrhage had occurred so rapidly that there had not been time for the circulating blood to take up any appreciable amount of fluid from the tissues, and that the blood in circulation while greatly reduced in volume was as yet unchanged in consistence. On the day after the operation the red cell count was 2,800,000 and the hemoglobin measured 58 per cent. It is interesting to note that although, before the operation, the red cells showed no material change in concentration, the circulating leukocytes had already increased to 35,000 per cubic millimeter. That rapid, severe hemorrhage is followed by a rise in the number of leukocytes and in the percentage of polymorphonuclear cells is well recognized; but we have been able to find no mention of the fact, illustrated in the present case, that this increase in the leukocytes occurs much earlier than do the other characteristic blood changes, namely, the fall in the number of red cells and in the percentage of hemoglobin.

Spontaneous rupture of the acutely swollen spleen is a rare occurrence, but has been encountered in the course of various fevers. In tropical malarial fever it has been seen in a considerable number of cases. More rarely it has been observed in typhus, relapsing, and typhoid fever. In the case of the last-named disease Melchior[1] has been able recently to collect but twelve authentic instances of such spontaneous rupture.* Since his careful review of the subject no further cases have appeared in the literature. The rarity of this complication in typhoid fever may be further shown by the following statistics: Curschmann[2] found two instances of it among 577 autopsies in cases of typhoid. Among 2000 typhoid autopsies in the Munich Pathological Institute it was observed five times (one of these was in a case of abscess of the spleen).[3] Among 474 fatal cases of typhoid observed in St. Jacob's Hospital in Leipzig between the years 1880 and 1907 no instance of rupture of the spleen was seen.[4] [5]

Bryan, of Richmond, Va., has reported an interesting case of

* Melchior's collection includes 13 cases, but one of these (Case IX) obviously cannot be regarded as an instance of *spontaneous* rupture.

spontaneous rupture of the spleen in the course of typhoid fever and has attempted to assemble all the reported cases, but in his collection of twenty-eight cases he has included indiscriminately cases of ruptured spleen in typhus, relapsing, and malarial fevers as well as typhoid.

All of the twelve cases of spontaneous rupture in typhoid collected by Melchior occurred in males. Ten of these were adults; two were boys, aged respectively eight and ten years.

As regards the time of the disease at which the rupture occurred: in five of the thirteen cases (including our own) the signs of rupture appeared during or at the end of the second week; in two cases during the third week; in one at the end of the fifth week; in one during convalescence, and in one during an apparent relapse. In three cases there is no information upon this point.

The site of the rupture is mentioned in seven of the thirteen cases. In three instances this was in the region of the hilum; in two cases, near the lower pole; in one on the diaphragmatic surface, and in one (our own) along the posterior border. Usually the tear has been linear. In one case it was stellate; in one angular; in another it extended almost around the spleen near its middle. In most of the cases the tear has involved not only the capsule but the parenchyma as well. In our own case, however, and in that of Kammerer the tear was confined to the capsule; but in spite of this fact the hemorrhage in both cases was enormous.

The duration of the symptoms in the cases of rupture of the spleen has varied from a few hours to two or three days. In Erichsen's case death is said to have occurred "in a few minutes." In nine of the twelve cases collected by Melchior the condition was recognized only at autopsy. In the three remaining cases (Kammerer, West and Dudding, Bryan) the rupture of the spleen was discovered in the course of an operation done for supposed intestinal perforation. None of these cases recovered.

The symptoms of rupture of the spleen fall into two quite distinct groups: (1) the local symptoms of the rupture and of irritation of the neighboring peritoneum by the extravasated blood; and (2) the general symptoms of severe internal hemorrhage. In most of the cases described, pain seems to have been the first

symptom, although the location and character of the pain have usually not been given in much detail. In our own case there was severe pain referred to the splenic region and also very severe pain in the left shoulder and in the left supraclavicular fossa. In West and Dudding's case the pain is said to have been referred to the central part of the abdomen. In addition to the pain there has usually been some tenderness and muscular rigidity in the left upper quadrant of the abdomen. In one of Chrostowski's cases the tenderness was extreme. The general symptoms, due to the progressive loss of blood, have been increasing collapse, pallor, a very rapid pulse with falling temperature, restlessness, thirst, etc. In one case (Bryan[6]) instead of a fall in temperature there was a rise to 106°.

The diagnosis of rupture of the spleen in the course of typhoid fever rests upon the association of the signs of local trouble in the left upper quadrant of the abdomen (pain, tenderness, muscular rigidity), with the evidences of progressive internal hemorrhage. In most cases the diagnosis ought not to be difficult if only the possibility of the occurrence of such a rupture is borne in mind. In our own case this possibility was suggested by the fact that the spleen had been recognized as being unusually large for the early days of typhoid fever. The difficulties of diagnosis will naturally be greatly increased in cases which are already gravely ill or in which delirium or great apathy masks the local symptoms. In the three earlier cases operated upon the condition suspected was that of intestinal perforation or perforation and hemorrhage.

Prognosis. Although all of the twelve previously reported cases have died, the evidence in our case that the first rupture occurred three days before the appearance of the symptoms which led to the operation, suggests the possibility that such a rupture may in rare instances be followed by spontaneous recovery. In general it may be said, however, that the only chance of recovery lies in the prompt recognition of the condition and in immediate operation. In most instances the loss of blood has been so rapid and severe that the delay of even a few hours would greatly imperil the chance of recovery; so that in any case in which there is a reasonable probability that the condition is one of rupture of the

spleen the safest procedure would seem to be the making of a small exploratory incision under local anesthesia, as was done in the present case. If a rupture is found there seems to be no question that the prompt removal of the organ is greatly to be preferred to any attempt to check the bleeding by merely packing the wound in the spleen.

A summary of the twelve cases already reported is as follows:

1. Nückel,[7] 1839. A robust man, aged twenty-five years; seized with diarrhea fourteen days before death. Two days before death took to his bed with abdominal pain. Then followed collapse, pallor, sweating, cold extremities, and death. Autopsy: large, soft spleen, in the lower part of the outer surface of which was an angular tear three to four lines wide. Left hypochondrium filled with blood which extended throughout the left side of the abdomen as far as the true pelvis. Numerous ulcers in the ileum.

2. Heimann,[8] 1843. In an account of a typhoid epidemic in Moscow is a brief reference to a case in which the enlargement and softening of the spleen was so great that the capsule, stretched to its utmost, finally burst and the softened material almost filled the left side of the abdominal cavity.

3. Erichsen,[9] 1861. A vigorous man, who had passed through typhoid fever and was almost ready to be discharged, suddenly collapsed and died "in a few minutes." The autopsy showed the abdomen to be filled with an enormous quantity of liquid and clotted blood. The pancreas was surrounded by a mass of clot as large as a child's head, which extended to the hilum of the spleen. The spleen formed a flaccid sac seven inches in diameter composed of grumous, confluent, livid-red parenchyma in which no trace of normal splenic structure could be seen. In the region of the hilum were three or four tears about one inch in length. Liver cirrhotic, enlarged, and anemic.

4. Delafield,* 1875. Boy, aged eighteen years; two weeks ago caught cold; seized with cough, fever, coffee-ground sputa; a little pain in the right side of the chest. Worse every afternoon. No diarrhea, headache, nor epistaxis.

October 27. Tongue clean, pulse 100; temperature $99\frac{3}{4}°$; bowels regular; urine 1010, no albumin. Coarse rales over both lungs.

October 29. Pulse 100 to 112; temperature $99\frac{3}{4}°$ to $102\frac{1}{4}°$.

October 30. Pulse 114 to 122; temperature 100° to $103\frac{1}{2}°$.

October 31. Pulse 104; temperature $100\frac{1}{4}°$.

November 1. Pulse 96 to 120; temperature 99° to $98\frac{1}{2}°$.

November 2. Pulse 98 to 120; temperature 99° to $98\frac{1}{2}°$.

* Through the courtesy of Dr. Delafield these notes were copied from his case book.

November 3. Has been improving; today sat up.

November 7. Complains of weakness; stays in bed.

November 10. Suddenly much worse. 2 P.M., pulse 145; temperature 104¼°; 8 P.M., pulse 144; temperature 105½°.

November 11. 2.30 A.M., was found in the hall dying. Died 3 A.M.

Autopsy. Brain, slight increase of serum beneath; heart normal; lungs, moderate bronchitis; liver normal. Spleen fourteen ounces, a very large rupture extending all around it at about its middle. In the peritoneal cavity a large amount of blood. Large intestine normal. Along entire length of ileum solitary and agminated glands very much swollen and a very few of them ulcerated. Small nodules in mucous membrane. Mesenteric glands very much swollen.

5. Wittmann,[10] 1876. Boy aged ten years. Admitted to hospital on sixth day of illness. Persistent high fever, delirium and bleeding from mouth and bowels. Tenderness over cecum and spleen. Splenic dulness much increased. From eighth day of illness on, increasing tenderness of abdomen, especially in region of spleen. On thirteenth day rapid fall of the persistently high temperature to subnormal, symptoms of acute collapse, and death.

Autopsy. Abdominal cavity contained 1½ pounds of liquid and clotted blood. Spleen enlarged fourfold, soft and pale. On the outer border a tear 1 inch deep and 2½ inches long, beginning near the hilum, running to the outer border and ending on the upper surface. A second, shallower and shorter tear began near the hilum, where it was joined with the first tear and extended down toward the tip of the spleen. Peyer's patches swollen and in part ulcerated. Mesenteric glands much enlarged.

6. Chrostowski,[11] 1885. Blacksmith, aged twenty-seven years. Had been ill several days when first seen. Temperature 40.3° C.; pulse 100; respirations 24. Two days later became very delirious, desperately attempting to get out of bed. Great tenderness in region of spleen. High temperature and rapid pulse and respirations. Abdomen enormously enlarged. Became unconscious during the night and died next morning.

Autopsy. Spleen six times its usual size; the outside covered with thick, dark blood. Vertical rupture of spleen 8 to 10 cm. long.

7. Chrostowski,[11] 1885. Male, aged eighteen years. Ill in bed six days before admission to the hospital. On twenty-second day, the temperature still high, patient delirious. Next day temperature fell to normal and patient seemed better, but on following day he died.

Autopsy. Spleen considerably enlarged and surrounded by thick, coagulated blood. Spleen showed a rupture of the capsule 3 cm. long, which extended into the splenic pulp.

8. Aaser,[12] 1898. Man, aged twenty years. Typhoid fever of fourteen days' duration. Patient died a half hour after admission to hospital.

Autopsy. Showed a rupture of the spleen so extensive that a portion of the organ was almost completely severed from the rest.

9. Kammerer,[13] 1902. Patient in third week of typhoid fever. No trauma. Sudden restlessness and signs of internal hemorrhage. Diagnosis of intestinal perforation. Operation. Large amount of blood in belly. Intestine intact. Greatly enlarged spleen surrounded by clot. Capsule showed a tear four inches long through which the splenic tissue protruded. Extirpation of spleen. Death after twelve hours. The rupture involved the capsule only.

10. Craig,[14] 1904. Soldier, aged twenty-three years. Illness of eight days before admission to hospital on September 12. Temperature reached normal before October 3. On that day patient felt cold and sleepy. Temperature subnormal. Slight delirium. Next day severe pain referred to left hypochondrium. This pain increased on following day. Gradual collapse and death on October 7.

Autopsy. Typhoid ulcers in ileum. Coils of small intestine adherent and covered with purulent exudate. Appendix inflamed. Spleen greatly enlarged (20 by 11 cm.) and surrounded by a great mass of blood. Tear in spleen 3 cm. long and 1 cm. deep, from which the splenic tissue protrudes.

11. West and Dudding,[15] 1906. Soldier, aged twenty-five years. Admitted to hospital on third day of illness. Fever ran mild course with few symptoms until the ninth day (March 3), when at 8.45 A.M. he complained of severe pain in the middle of the abdomen. When seen fifteen minutes later he was in a collapsed condition, somewhat restless, with a rapid, weak pulse and with the abdomen tender, distended, and tympanitic. Perforation suspected. Operation. Abdomen filled with blood. No perforation discovered. Spleen suspected as being the source of the bleeding, but because of the bad condition of the patient the abdomen was closed. Death ten minutes later.

Autopsy. Spleen greatly enlarged, weight 2 pounds and $2\frac{1}{2}$ ounces. Capsule showed a tear three inches long on the diaphragmatic surface and was extensively separated by clot. Typhoid ulcers in ileum and colon.

12. Bryan,[16] 1909. Man, aged thirty-one years. Admitted to hospital November 2, having been ill for one week with fever and headache. Complained of some pain on left side under ribs. Ran a persistently high fever for the next twelve days. No trauma. On the evening of November 14 the temperature became higher than usual (106°) and the pulse very rapid and weak. The face was pinched, nose and extremities cold, there was moderate dyspnea. The belly was hard, resistant, and tympanitic, but not distended. Diagnosis. Perforation and hemorrhage. Operation. The abdomen was opened along the outer border of the right rectus muscle. No perforation found although thickened Peyer's patches were evident. Blood in large quantities was found in the pelvis and in the region of the spleen. Spleen removed. In spite of saline infusion and other measures

to combat the shock and loss of blood. death followed one hour later. The spleen measured 18 by 9 cm. and weighed $14\frac{2}{3}$ ounces. The rupture, situated at the lower pole was stellate, everted, and crater-like. It covered an area 2.2 by 3.8 cm., and extended into the tissue of the organ.

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DISCUSSION

DR. THEODORE C. JANEWAY: Examination of the peripheral blood by the ordinary methods soon after even large hemorrhages will not reveal much change. It takes considerable time for the blood to replenish its bulk, and my experience is that an interval of about three days usually elapses after large hemorrhages before there will be found in the peripheral blood a reduction in the red count and in the hemoglobin. There seems to be no way to estimate the bulk of blood loss in internal hemorrhage at the time of the accident except by observation of the facies.

DISSEMINATED MILIARY TUBERCULOSIS OF LUNGS AND SKIN

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The diagnosis of miliary tuberculosis in the very young is difficult. In the lungs, for instance, without consolidation and without cavity, miliary tuberculosis may be strongly suspected, but not easily proved.

I submit herewith two helps to the diagnosis—one, of the lungs—the *x*-ray; the other of the skin—the eruption. The first case selected for illustration shows both diagnostic signs and will be submitted complete. The best recent *x*-ray apparatus has made it possible to produce the accompanying pictures, which speak for themselves. In six cases of infants and young children suspected of disseminated miliary tuberculosis of the lungs, the *x*-ray has coöperated with other tests to decide the diagnosis. For illustration of what can be done, the best *x*-ray plate has been selected, the best print made from it, and the best result obtainable here presented (Fig. 1).

The second help to the diagnosis of general miliary tuberculosis in the young is general miliary tuberculosis of the skin. The localized lesions of the skin so often described, are not here meant (Figs. 2, 3, and 4).

Case I.—General miliary tuberculosis; involvement of skin.

Dorothy K., aged two and a half years, was admitted to the Presbyterian Hospital with the diagnosis of pneumonia. The case presents the following points of interest: (1) The patient had the appearance and the chart of a child sick with pneumonia, but with the physical signs of

bronchitis. (2) The exact diagnosis was made by *x*-ray (lungs) (Fig. 5). (3) There was an unusual skin eruption of disseminated miliary tuberculosis (Figs. 2, 3, and 4). (4) A necropsy completed the record and confirmed all previous findings.

FIG. 1.—General miliary tuberculosis. Radiograph of thorax of Rosie R., aged eight years. Tubercle bacilli recovered from the spinal fluid. No necropsy.

1. Physical signs: As to the "look and chart" of pneumonia in this child, the temperature (T) was high and continuous, 102° to 105° F.; the pulse (P) was 130 to 160 per minute; the respiration (R) was 42 to 72; out of normal proportion to the pulse; the R-P ratio was "disturbed." "When the R-P ratio departs from the normal of $\frac{1}{4}$ and approximates $\frac{1}{3}$, look for pneumonia" (O'Dwyer). It is to children that I would apply this; it is not so valuable in adults.

It would be exceptional for a pneumonia patient to remain in hospital a week developing a severe febrile reaction, without revealing some signs of

FIG. 2.—Miliary tuberculosis of the skin. Papulovesicles; hemorrhagic crusts (umbilicated). Properly, necrotic tuberculid.

FIG. 3.—Tuberculosis of skin; papulovesicular; crusts (umbilicated); hemorrhagic. Properly, necrotic tuberculid.

consolidation. Presumably all clinical men will think there is here shown good reason for the diagnosis of tuberculosis. That is granted. For exact diagnosis by means of new and high-grade mechanical appliances, however, we may still contend.

2. Exact Diagnosis by *X*-ray: At the last meeting of this Association I presented in discussion of Dr. Sewell's paper an *x*-ray plate showing clearly disseminated miliary tuberculosis of the lungs without consolidation; also without excavation (Fig. 1). At this time I am prepared to submit the *x*-ray plates of six cases including the first shown. Two of the cases have been confirmed by necropsy (the one here shown being included), one has been corroborated by inoculation into the guinea-pig, one was confirmed by examination of an excised gland; others by finding bacilli in the throat swabs, etc., until we can be rationally certain that our *x*-ray findings are reliable and trustworthy.

FIG. 4.—Miliary tuberculosis of skin; papulovesicular; hemorrhagic; crusts (umbilicated). Properly, necrotic tuberculid.

3. Skin Eruption: Miliary skin tuberculosis, necrotic skin tuberculid —the names suggested are sufficiently descriptive. This is an unusual though not rare lesion. In the Presbyterian Hospital three cases have been seen. I personally have seen but two (Figs. 2, 3, and 4).

The character of the eruption is papulovesicular, perhaps more vesicular from the first. On the neck, in the above case, the vesicles were more like sudamina, a little larger, though not as large as the vesicle of chickenpox. They were thickly clustered in the neck. Later there developed a hemorrhagic zone about the vesicle and a subsequent drying and crusting in the middle of the lesion. The completed individual lesion was about 2 mm. in diameter. This stage is figured in Pfaundler and Schlossmann in an excellent picture, to which the reader is referred. The illustrations are colored and are the only ones known to us. The accompanying photographs of the present case, in black and white, show to good advantage (Figs. 2, 3, and 4). The rash was on all skin surfaces, including soles, palms, and

scalp, with more about the mouth, anus, and buttocks. The superficial lymph nodes were enlarged everywhere; the liver was enlarged. Naturally the case attracted a good deal of attention. Colleagues who were called in to see the case expressed their views, one suggesting syphilis, another chickenpox. The rash is said to have been evident three days before entrance, appearing first about the mouth, neck, and chest.

Fig. 5.—Miliary tuberculosis of lungs. Same patient had also miliary tuberculosis of skin (necrotic tuberculid).

4. Necropsy: The brain was not examined; tubercles were found in the lungs, spleen, kidneys, liver, etc. Tubercle bacilli were found in clumps in the blood of the heart in any casual smear. Smears taken from the skin vessels showed such quantities that the spread-out carmin was faintly

pink from the stained bacilli. The case was acute, which may have determined the character of lesions.

It is interesting to note that the structure of the tubercles was not the usual structure; in fact, strictly speaking, they were not tubercles at all. More properly speaking, the lesion was necrotic tuberculosis ("tuberculid"); there was no tissue reaction, merely melting down into necrosis wherever tubercle bacilli stopped and began to grow. There were no connective-tissue reaction, no giant cells, no surrounding zone of epithelioid and mononuclear wandering cells. "There were just necrotic areas filled with tubercle bacilli. In none of the zones were found evidences of protective reaction" (Dr. Lamb). Simply larger and smaller areas of necrosis, lymph nodes, and tonsils containing the same.

Six cases are shown in the *x*-ray plates. All of the patients came into the hospital with the evidence in favor of acute pneumonia, the chart bearing out the general suggestion and appearance of the disease. The *x*-ray was really the first means of positive diagnosis, being subsequently confirmed by finding tubercle bacilli.

Tuberculous eruption on the skin, necrotic tuberculid, disseminated miliary tuberculosis of the skin, suggest in their names the characteristics of the lesions under consideration.

Case II.—General miliary tuberculosis involving the skin in a child aged eighteen months. Died. No autopsy.

Kate N. entered the Presbyterian Hospital with the diagnosis of pneumonia. The onset was abrupt three days before, with drowsiness, fever, cough, and a peculiar unrecognized rash.

Examination showed a temperature of 101° to 103° F., rising to 105.5° F. at or just before death, cough, coarse rales over both lungs, harsh breathing and voice over irregular areas, restlessness, flaring nostrils—satisfactory evidences of pneumonia. As there was no *x*-ray in common use at that time, no radiographs can be shown. There was no autopsy. No bacilli were found.

Skin Eruption: In order of time this case was the first case that had come under the observation of the staff and was not recognized until an excellent colored illustration in Pfaundler and Schlossmann was noticed. It is important to have this case in mind in deciding on skin eruptions, for those who see one case and recognize its character will never make a mistake. Witness the fact that the two cases accompanying this were recognized instantly by those who saw the first, and by no others present.

The eruption was discrete, papulovesicular, later drying, "topped with a scab," about 2 mm. in diameter, and, as the recorder says, "suggestive of chickenpox, except that the papules are small."

An expert from the Board of Health pronounced it a late stage of chickenpox, thus explaining why they were so small.

The lesion is called by Pfaundler and Schlossmann "necrotic tuberculid."

Case III.—Pulmonary tuberculosis and skin tuberculids.

John H., aged fifteen months. This patient also came to hospital with the diagnosis of acute pneumonia. The patient died; no necropsy and no radiographs made, but the tissues of the skin lesion were inoculated into guinea-pigs and proved to be tuberculosis.

The patient was in hospital five days, in a dying condition all the time. The lungs showed rales everywhere, bronchial voice and breathing, harsh in nature.

The main interest centres about the skin lesion, small pinhead-sized and a little larger papules with small necrotic centres. There were a few on the arms and legs, a few on the back and front of the trunk, also one or two on the thighs. There were a few small ecchymotic spots on the thighs. The diagnosis was pulmonary tuberculosis, and on the skin, tuberculids. When engrafted in the guinea-pig, typical tuberculosis in the internal organs was developed.

Case IV.—General miliary tuberculosis of lungs; *x*-ray; autopsy.

William F. (colored), aged ten months, entered the hospital with the diagnosis of pneumonia. There were fever, apathy ("dopey"), R-P ration disturbed, 1 to 3; respiration, 36 to 50 per minute; pulse, 110 to 150 per minute, irregular; temperature, 100.5° to 102.5° F.; discharging ear; vomiting -manifestly a very sick child; no consolidation of the lung; no tubercle bacilli found, no history of rales in the chest. The diagnosis was suspected from the history and chart but not confirmed until the *x*-ray showed it clearly and unmistakably. This was one of the best proofs of the value of the *x*-ray. As to rales, they were probably to be found at favorable moments, after a long interval of uninterrupted quiet. The hospital interne states that the lungs were clear in front and behind. Spinal fluid was perfectly clear. Noguchi-Wassermann test of blood and spinal fluid was negative.

This case, also entered as one of pneumonia, was then believed to be tuberculosis from the history and chart, and the diagnosis was confirmed by the *x*-ray and at last by autopsy. The radiograph was one of the best of the series.

Case V.—Diagnosis on admission, acute tuberculous bronchopneumonia. General tuberculosis. Died. No autopsy.

Vieto S., aged three years. This case is one in which there was good ground for believing that there was tuberculosis, and the *x*-ray was convincing; there was also confirmation later from the tissue of a superficial gland.

Case VI.—Diagnosis on admission, general bronchitis, probably tuberculous. *X*-ray convincing. No corroboration. No necropsy.

Dan B., aged six years. This case on admission was one that suggested pneumonia, general bronchitis, and at length the conviction that it was probably tuberculosis. The point of interest was the convincing *x*-ray picture. There was no corroborating evidence of tuberculosis, but the *x*-ray was so good that there could be no feeling of doubt.

The child had had measles, whooping cough, and pneumonia. He entered the hospital with a cough which had been active for two weeks, and there was evidence of an acute fever chill and fever, no expectoration, no vomiting. Patient had been treated for malaria. In the lungs were fine, scattered, "squeaking" rales.

There were thought to be certain localities in which the breathing sounds indicated a moderate condensation of the lungs, but the *x*-ray did not corroborate it. There was no record of positive evidence of consolidation. The patient was several weeks in hospital, and the *x*-ray was the only convincing testimony outside of the ordinary clinical features.

Case VII.—Entered as pneumonia. Diagnosis by *x*-ray. Tubercle bacilli found in spinal fluid. No necropsy.

Rosie R. This eight-year-old child was in the hospital twenty-five days, running the course of an old-fashioned consumptive. The history on admission, however, suggested pneumonia, cough, expectoration, blood-stained, sticky expectoration, stabbing pains in the chest, night sweats, and loss of weight.

The previous history was that of measles at two years, bronchitis at seven. The interest in the case centres in the *x*-ray testimony. It was a convincing picture and was corroborated by finding tubercle bacilli in the spinal fluid (Fig. 1).

Case VIII.—Diagnosis on discharge was general miliary tuberculosis of the lungs. *X*-ray. Improved.

John S., aged nine years. The interest in this case rests on these points: A suggestive previous history; a positive *x*-ray picture; "tubercles on the lungs;" good, general condition; discharged, having no fever and apparently thriving fairly. Sent to the country for still further improvement.

Previous History. No significant family history or surroundings. Previous illnesses, whooping cough, measles, and indefinite history of tumors which seem to have been tuberculosis of the lymph nodes just over sternum and neck. This patient was observed in good hospitals just before coming to the present one, and nothing special was discovered in the lungs. In one particularly good hospital, where the facilities for *x*-ray would probably be excellent, nothing was sought by *x*-ray; at least there was nothing said about it.

Examination. Bright boy; does not look ill; ears and cheeks bluish-red; not dyspneic; slightly cyanotic; mentally alert; no noteworthy scars;

tongue clean in the middle line; lips very red; cervical and inguinal glands enlarged; lungs and abdomen negative; extremities and hands bluish; veins of neck enlarged; a few moist rales, most of which clear up on deep breathing; while in hospital, up and about, comfortable, always cyanosed, notably about the ears and lips, also finger nails. Fluoroscopic examination confirms *x*-ray plates described above. Patient went to Loomis Sanatorium. Father reports glands are smaller. Clinical diagnosis, cervical tuberculous adenitis.

Discussion. There is still an added interest to this case: the human interest in a case that by all laws and experience is doomed, yet has gone out of the hospital with lungs thickly studded with miliary tubercles. To be sure, without the recent new appliances above alluded to, the diagnostician might have thought he had made a mistake; the case then would have passed as undetermined and the memory need not concern itself trying to learn anything from it. Whether the further history of this case is ever written cannot now be said. This may be the final outcome—by the use of the *x*-ray many such histories may accumulate and the profession learn that they have for years been overlooking cases of disseminated miliary tuberculosis of the lung. What the Wassermann reaction is to syphilis, the *x*-ray promises to be to the diagnosis of lung tuberculosis in children.

These three cases of skin tuberculosis present the characteristic features thus far met in our experience and most of those recorded by Tileston in his larger experience.

The most profitable impression to carry away from this reading is that the cases present to the experienced observer the mental picture of pneumonia, but the physical signs of bronchitis. At this point the physician may be unable to procure any reliable testimony for exact diagnosis; and until a good *x*-ray picture has been obtained he may but conjecture, and he may never know whether or not he has made the correct diagnosis. Next to an autopsy the *x*-ray gives the most intimate knowledge of the lesion of the child's lung.

Skin eruptions in the feeble and non-resistant are not rare, but are mostly overlooked. The lesion is mainly necrotic, resulting in vesicles. There may be a stage of papulovesicle preceding

this. The cases here cited are distinctly acute. Our experience leads us to prefer the term given to the lesion by the authors, Pfaundler and Schlossmann, "necrotic tuberculid."

"The fatal result in infants is probably only another manifestation of the more pernicious course of tuberculosis in general in the first years of life."[1]

Briefly stated, the modern *x*-ray apparatus, next to an autopsy, furnishes the most valuable insight to the lung lesion of infants and young children.

Eruption of miliary tubercles furnishes a pathognomonic sign for diagnosis and a valuable, almost conclusive, point for prognosis; that is, the lesion is nearly always associated with a fatal form of tuberculosis in the young child.

The histology varies with the acuteness of the invasion. The above cases were of the acute type and the vesicles (necroses) were the first revealed lesion. It may be that slower developing lesions would disclose the different types described, viz., "papulosquamous" and "papulonecrotic" tuberculids, described by Darier and Boeck in 1896. Bacilli are found frequently in the blood and the eruption and the lesion is probably always embolic.

Among the characteristics of the individual lesions may be mentioned the *size*, that of a rose spot in typhoid fever, topped by a tiny *vesicle*, surrounded sooner or later with a congested or hemorrhagic *zone*, with the formation of a *crust*, which, when removed, leaves a little *pit*. The skin lesion is to be differentiated from that of chickenpox, molluscum contagiosum, and from syphilis.

Experience with this eruption is like that with scurvy in infants —once seen the lesion cannot be again overlooked.

DISCUSSION

Dr. S. Solis Cohen: In what proportion of the cases may such skin lesions be found?

Dr. Northrup: I can only reply to Dr. Solis Cohen that I do not know; I have seen only these three cases in my whole life.

[1] Tileston, Arch. Int. Med., July, 1909, iv, 21.

FACTORS WHICH MAY BE CONCERNED IN CAUSING HYPERTROPHY OF THE THYROID GLAND, AND THE EFFECT OF EXCISION OF THIS ORGAN UPON OTHER OF THE DUCTLESS GLANDS

By WILLIAM STEWART HALSTED, M.D.
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(By Invitation)

It is a high compliment to be invited to speak before this Association, and I appreciate the honor to myself which has been conferred by your Chairman, Dr. Barker.

The time allotted is so short that I cannot do more than indicate in merest outline a few of the problems which have presented themselves in the course of our study in animals and the human subject of the functions of some of the glands of internal secretion.

Twenty-five years ago, in the course of experiments upon the dog, undertaken chiefly with a view to determining the cause of death after operations upon the thyroid gland, I was surprised to find that excisions or transplantations or simple manipulations of the thyroid lobe were, after a time and almost invariably, followed by increase in the size of the remaining portions of the gland, wherever situated.

Examination of the hypertrophied tissue revealed the most unexpected and astonishing histological picture, a structure so different from the normal gland that not one of the several eminent pathologists in this country and abroad, to whom I showed the sections, was able to identify it. The histological changes which resemble those found in exophthalmic goitre are now so well known as not to require mention at this time. With few exceptions this

hypertrophic picture made its appearance within twenty-two days after operation of any kind upon the thyroid gland, and even in its most advanced type was observed as late as ninety-five days after operation.

My observations have been confirmed by many, most carefully and convincingly by Marine, and the hypertrophy has generally been regarded as compensatory.

In my original article I expressed the view that possibly some form of auto-intoxication might account for the hypertrophic changes, and for some years have thought that the hyperplasia of the remaining thyroid tissue which has followed excision of a portion of the gland might possibly be due to infection of the wound, and for the following reasons:

1. The increase in the size of the remaining thyroids and the degree of hyperplasia as indicated by the histological picture seemed to bear no relation to the amount removed. The excision of so little as one-fourth of one lobe might be followed by great increase in the size of both lobes, and by the histological changes which characterize hyperplasia.

2. In 1888 I found that hypertrophy of the thyroid glands of dogs occurred after the injection of several cubic centimeters of a bouillon culture of staphylococcus aureus into the peritoneal cavity, and also when a mild form of peritonitis had been produced in these animals—a peritonitis which was not rapidly fatal.

3. Experiments conducted in 1906 and 1907 in the Hunterian Laboratory seemed to indicate that for the successful transplantation of a parathyroid glandule a considerable deficiency must be created.

4. Twice in the course of the past five years I have had opportunity to examine the remaining lobe of the thyroid gland after excision of the other in dogs whose wounds had healed throughout without suppuration and have noted that there was no hyperplasia of the former.

5. From a restudy of the report of my experiments on extirpation of the thyroid gland made in 1888, I find that for the major part of the experiments the wounds of the dogs were left open, and that after twenty-two days, with few exceptions, there was hypertrophy,

macroscopic and microscopic, of the remaining gland in the animals whose wounds were permitted to heal by granulation, whereas when the wound healed *per primam* the hyperplasia of the remaining thyroid tissue developed perhaps less regularly and not to the same extent.

6. Manifestations of hyperthyroidism may develop promptly after tonsillitis, appendicitis, pneumonia, typhoid fever, and other infections.

Last October, I proposed to Dr. Hunnicutt that he undertake a series of experiments with a view of determining the matter definitely. Observing aseptic precautions in the strictest manner, Dr. Hunnicutt has made a large number of experiments on dogs, and we are able to report that in none of the thyroids thus far examined has there been the slightest evidence of hyperplasia. The average time allowed to elapse between the removal of the first and second lobes was fifty-five days, the shortest interval being thirty and the longest eighty-one days.

That, nevertheless, there is such a thing as true compensatory hyperplasia of the thyroid gland is proved, I think, by my experiments in transplantation of the parathyroid glandules which were conducted with the strictest aseptic precautions. Thus when both thyroid lobes and the four parathyroid glandules have been removed and only a film of thyroid transplanted with one parathyroid body, this film hypertrophies enormously, and on microscopic examination displays the typical changes of extreme hyperplasia. In one instance the graft was examined fifteen months after operation.

If it should become a definitely established fact that true compensatory hyperplasia of the thyroid occurs only after the removal of a considerable part of this gland and that infection has been responsible for most of the hypertrophies hitherto recorded, investigations are then made possible which could not be undertaken to any purpose if hyperplasia might be expected to follow operative interference of almost any sort upon the thyroid lobe.

Although expecting that in wounds which healed by first intention hyperplasia might not develop after excision of small portions of one thyroid lobe, it surprised me to find from this year's experiments that so much as one and a half lobes may be removed without appreci-

able effect upon the remainder of the gland, and for the moment my interest in the search for an explanation of the entire absence of any sign of hypertrophy in the experiments of the past winter is as keen as it was years ago to explain the invariable hypertrophy which followed almost any sort of operative interference with the glandula thyroidea. Dr. Marine, replying a few days ago from Vienna to a letter in which I asked for his opinion, writes: "I am anxious to know whether you used iodine in the sterilization of the skin. This, as you know, inhibits to a marked degree compensatory hyperplasia following partial removal just as it does any physiological outgrowth. After trying all sorts of ways to check your 1888–1889 results, we always got exactly what you then reported, and I shall have to have very conclusive evidence before being convinced that your results obtained in 1888 could be explained on the basis of wound infection."

In most of our experiments the skin has been disinfected with iodine, but in several instances it was not.

Moreover, in dogs operated upon (partial thyroidectomy) without precautions and whose wounds were left open there was, greatly to my surprise, not the slightest indication of hypertrophy of the remaining lobe after thirty days.

I am wondering if possibly the vaccination against distemper can have had an influence in suppressing the hyperplasia. Except for the use of iodine as a disinfectant for the skin and the vaccination of most of our dogs, the conditions this year seem to be essentially the same as they were in 1888.

Should we find that, as a rule, three-fourths or more of the entire gland must be removed before the hyperplasic changes develop, this will be additional evidence to strengthen our belief that the thyroid gland is normally in a state of relative inactivity, and that it is an organ with great reserve power, capable of responding promptly, almost instantly, to certain stimuli.

Of particular interest to me in this connection are the experiments, just published, of Dr. Reich and Prof. Blauel, of Vienna. They find that in rats, whose thyroids normally have cuboidal epithelium, compression of the trachea is followed by flattening of this epithelium to an extreme degree. If the oxygen-deprivation

induced by the obturation of the trachea should prove to be the cause of the regressive or hypertrophic changes, might we expect to find that the colloid goitres which produce a great degree of tracheal stenosis are less likely to become Basedowified than those which are not accompanied by symptoms of suffocation?

Among the queries which present themselves at the moment are the following:

1. Must a deficiency be created for the successful grafting of ductless glands? Biedl claims to have successfully transplanted two parathyroid homografts in a dog which had not been deprived of any of its parathyroids. To justify his position, he states that all depends upon how long a transplant must live in order to be called a successful one. It seems to be an unchallenged proposition that a transplant cannot live unless it is functioning. But what is ment by functioning? Are tissues growing *in vitro* performing a function? Are the spirals of elastic tissue which we wind about the aorta functioning for a time? For about two months these spiral bands seem to live and continue to constrict the artery, but in six months they are almost absorbed.

2. What proportion of both thyroid lobes is it necessary to remove in order to produce hyperplasia of the remainder? The removal of one and one-half lobes has not been followed by hypertrophy in our experiments of this year.

3. Can a graft live without showing the hyperplastic picture? In other words, will a graft be absorbed unless the deficiency created is so great that hyperplasia must develop? Should the fact that a surviving graft retains the normal structure be taken as evidence that it will be absorbed (that its life will be of short duration)? And could a graft with such dubious existence be stimulated to hypertrophy and to prolonged life by the introduction of conditions which might demand of the thyroid increased function?

If we are still in doubt as to the cause of the hypertrophy of the thyroid glands in our experiments of twenty-five years ago, and are unable to explain its entire absence in our dogs of this past winter, after making scores of experiments to determine the effect of the removal of part of one gland on the remainder of the same organ, how infinitely greater are the difficulties incident to the explanation

of the effects upon ductless glands other than the one surgically attacked?

Hypertrophy or enlargement of the hypophysis, for example, described by many authors as following thyroidectomy, has been observed in various parts of the gland; in the anterior lobe, in the pars intermedia, and even in the pars nervosa. There are conflicting views as to the changes which take place both as to situation and as to histological detail. By most investigators the formation of colloid is emphasized, and this has been interpreted by several as signifying a taking on by the hypophysis of the function of the thyroid; the colloid in the former replacing this substance lost in consequence of the thyroidectomy.

But when experimental hyperplasia of the thyroid takes place, the colloid, instead of being increased in the remaining hypertrophied lobe, is diminished or disappears altogether; and this being the case, it would seem strange that, after thyroidectomy, it should appear in compensating fashion in the pituitary gland. We think of the normal thyroid, with its large follicles filled with colloid, relatively dense and deeply staining, as being in a state of comparative inactivity or rest; and the histological changes which have been stimulated in one gland by the removal of another, have usually beeen considered as representing hyperactivity of this gland. But to me it appears unlikely that the colloid in the hypophysis which it is assumed makes its appearance in response to thyroid deficiency should signify hyperactivity of that organ, when the same colloid in the thyroid is found in abundance only in the comparatively inactive period of this gland.

It seems to be a natural inference that the loss of one gland of internal secretion should lead to the compensatory hypertrophy of another; and should colloid make its appearance in the eagerly observed unaccustomed places after the removal of a gland which normally is composed chiefly of colloid, the evidence for the compensatory nature of the change would seem to be so complete as to make further substantiation unnecessary. But I am quite sure that the evidence for the current view is not conclusive.

Is it not more probable that the elimination of the function of the thyroid may lessen, directly or indirectly, the demands on other

of the ductless glands and that the colloid changes noted in the hypophysis and parathyroids after thyroidectomy may signify hypo- and not hyperactivity of these organs?

A contribution by Kummer,[1] of Geneva, to the study of post-operative tetany, presented at the Twenty-fifth Session of the Congrès Française de Chirurgie, Paris, 1912, is worthy of unusual consideration. A woman, completely deprived of the cervical thyroids and parathyroids, was kept alive for two years.

The autopsy was made by Prof. Askanzy,[2] who found in the hypophysis changes which seem to be identical with those described by William G. MacCallum[3] as having been present in the hypophysis of one of my dogs fifteen months after the removal of both thyroid lobes and of the four parathyroids. This dog, kept alive for this long period by a parathyroid autograft only 14 mm. in diameter, died of tetany on the removal of the transplant.

Rarely again should there be an opportunity to study on the human subject the effects, after two years, of the complete removal of the thyroid and parathyroid glands.

We have never observed hypertrophy of the transplanted parathyroids even when total thyroidectomy and total parathyroidectomy have been done. I am not prepared, at present, to report the results of operations to determine the effect, if any, upon the thyroid of excision of the parathyroids; but I am not quite willing to accept as proved the observations of others who claim that

[1] Contribution à l'étude de la Tétanié postopératoire. Extrait des Comptes Rendus du 25° Congrès de l'association Française de Chir., 1912.

[2] Quotation from Askanzy: "*Hypophyse.* Les cellules chromophiles ou éosinophiles sont très abondamment développées, d'une richesse même extraordinaire. Par contre il n'y a pas d'augmentation de substance colloïde dans les amas cellulaires de l'hypophyse, comme cela se voit dans les hypophyses chez les myxoedémateux. C'est seulement près de la partie nerveuse d'ailleurs intacte, dans la zone intermédiare soit médullaire, que l'on constate quelques follicules a substance colloïde conformément a l'aspect ordinaire."

[3] Quotation from MacCallum: "The hypophysis shows rather distinct alterations. The pars nervosa is practically surrounded in the section by the pars intermedia which is perhaps slightly thickened and contains one or two alveoli full of colloid. The pars anterior is in part very deeply stained with eosin, but one portion, and that the major part, is sharply marked off from this eosin-stained tissue by its lilac color. It contains only a few of the bright staining cells, but for the most part is made up of swollen, faintly granular, pale stained cells. These resemble very closely the section obtained by Dr. Homans after injecting pilocarpin. The cleft in the glandular part of the hypophysis is here seen to open into the subarachnoid space." Halsted, Jour. Exp. Med., 1912, xv, No. 3, 209.

after thyroid lobectomy the parathyroids are stimulated to compensatory hypertrophy, forming follicles containing colloid. *Why should the excision of an amount of thyroid insufficient to bring about thyroid hyperplasia cause compensatory hyperplasia of the parathyroid glandules? And, granted that changes may have occurred in the glandules after thyroid lobectomy, should these consist in the formation of a colloid equivalent to the colloid of the thyroid alveolus if the thyroid-colloid disappears in cases of definite privation and if the accumulation of colloid seems to signify a state of normal or hyporather than of hyperactivity?*

Furthermore, if hypertrophy of the parathyroids really occurs after thyroidectomy, might it not be due to the unintentional destruction of some of the parathyroids, or even to infection of the wound?

I have never observed hypertrophy of a transplanted parathyroid gland. The tendency of these grafts, in my experience, is always to atrophy.

An enormous amount of experimentation must be done before these questions, which are in no sense remote, can be answered. There are hundreds of eager workers in this fascinating field at present who may add immensely to the confusion, before, from the chaos, order eventually can emerge and the simple laws be established of which perhaps we are not even beginning to dream.

Hypertrophy of the thymus gland has frequently been observed in Graves' disease, and from our observations during the past ten or eleven years of a considerable number of such cases in which the greater part of both thyroid lobes has been removed, we think there is reason to believe that the thymus atrophies in consequence of the operation upon the thyroid. The lymphocytosis gradually disappears, and in none of the earlier cases which have presented themselves this past year for examination has the thymus been skiagraphically visible. It would seem, therefore, that the thymus may be activated by the thyroid.[1]

[1] Support to this view is given by the results of the convincing experiments of A. L. Tatum reported since the reading of this paper (see Jour. Exp. Med., June 1, 1913). Tatum finds that in rabbits the thymus atrophies after excision of the thyroid gland.

DISCUSSION

Dr. W. G. MacCallum: Dr. Halsted's suspicion that the hyperplastic changes seen in the thyroids of his experimental dogs may have been due to wound infection possibly has an important bearing on the etiology of Graves' disease. Though a vast amount of work has been done in the study of the disease itself, no special attempts have been made to study the exact causes underlying the development of exophthalmic goitre; but Dr. Halsted's observations serve to recall the suggestion that some primary infectious disease may be back of it.

It is likely that in those instances in which the parathyroids of thyroidectomized animals have been said to have undergone colloid changes, the so-called parathyroid glandules were in reality aberrant thyroids.

Dr. Halsted: Dr. MacCallum's suggestion that so-called hyperplastic parathyroids containing colloid are in fact aberrant thyroid masses is probably correct.

THE ETIOLOGY, SYMPTOMATOLOGY, DIAGNOSIS, AND TREATMENT OF ACQUIRED DISPLACEMENT AND FIXATION OF THE STOMACH AND INTESTINES

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We wish to present in this article a series of observations on a group of cases of acquired fixation or displacement of stomach and intestines, some with definite local symptoms, other cases, which by their long duration, the vagueness of their symptoms, and their protean character have usually been regarded as cases of neurasthenia, psychasthenia, auto-intoxication, or nervous indigestion, but which in reality are due to definite organic change in the gastro-intestinal tract. These cases lie really on the borderline between medicine and surgery, and can only be properly appreciated by a comparison of the clinical findings with the operative results, although it is only after a most careful study that operative treatment is seen to be necessary in a considerable proportion of cases if a cure or improvement is to be hoped for. In our series were 32 cases of abnormal fixation or displacement of the stomach or intestines in which operative treatment was employed, and 54 cases which up to the present have not been operated upon. This autopsy *in vivo* has been a most important element in fixing the relative value of the clinical symptoms, and in our opinion progress in unravelling these cases can only come by close association of physician and surgeon, and the attendance by the former at the operation. Practically all these cases were of long duration, and the great majority had been treated either for functional gastro-intestinal disturbances, or for neurasthenia or psychas-

thenia during their period of ill health. A careful analysis of the clinical histories, however, showed that in the past in a certain proportion of the cases there had been acute attacks, usually regarded as acute gastritis or intestinal indigestion, gastralgia, etc., but which had been entirely forgotten in the lapse of years. On the other hand in a considerable proportion of the cases the most careful questioning failed to reveal any acute symptoms which might play a part in the etiology of these conditions.

Poised as it were between two forces, the pushing force of the respiratory apparatus acting through the diaphragm, and the lifting force of the muscles of the abdominal wall and of the pelvic floor, and definitely fixed at but a few spots, and loosely at that, the gastro-intestinal tract is singularly labile, singularly susceptible to change in position. Pulmonary hypertrophy and emphysema, pleural effusions, retraction of the lung, cardiac hypertrophy, pericardial effusion, tumors or enlargements of the liver, kidney, spleen, pancreas and mesenteric glands, of the pelvic organs, relaxation of the abdominal muscles or those of the pelvic floor, notably in women after childbirth, the loss of abdominal fat, especially if sudden, ascites, and the removal of the ascitic fluid, pregnancy and delivery, acute diseases associated with loss of weight and of muscle tone, as tuberculosis and typhoid, tumors arising in the stomach or intestines, etc., all will of necessity produce displacement of a greater or less extent in certain portions of the gastro-intestinal tract, but in the cases we have studied we will not include those due to changes in the pressure relations in the abdominal cavity, to weakening of the natural supports of the stomach and intestines by disease, to the pressure of new-growths, accumulations of fluid, or enlargement of organs, but we will confine our attention entirely to that group of cases in which the condition has been brought about by the traction or constriction of adhesions. In this consideration we will devote most attention to the clinical findings in the 32 operative cases, as in these cases the correctness or incorrectness of our clinical deductions could be verified by the operative findings. In these 32 cases, in 13 the cause of the displacement was undoubtedly a chronic appendicitis, although in many of these there were definite evidences of a perityphlitis or pericolitis as well; in 3 cases

the adhesions arose from the gall-bladder, although there had been no acute symptoms referable to that organ; in 5 cases the adhesions arose along the colon or cecum, the appendix apparently being involved only secondarily; in 1 the pancreas seemed to be the source; in 5 an ulcer of the stomach or duodenum; in 6 adhesions were found about the pylorus or the duodenum with no evidence of an ulcer; in 4 the adhesions followed previous operation, while in 3 they were secondary to malignant disease.

In these cases, of course, the right side is mainly affected, as it is here that we find the main source of these adhesions in the appendix and cecum, the gall-bladder, and the pylorus and the duodenum. In our series we had no cases due directly to tuberculosis, or to syphilis; probably certain of the gall-bladder and intestinal cases had their onset in preceding attacks of typhoid fever. Cecum mobile as the cause of stasis or displacement, due to torsion, we could not definitely determine, and, in fact, it is questionable whether the condition is pathological, as, according to some observers, it is present in more than 50 per cent. of autopsies. The question of the exact etiology of adhesions in the cecal and ascending colonic regions depends, of course, largely upon the interpretation of the findings at the time of operation, as in many cases the appendix is involved, and at the same time there are associated adhesions along the cecum and ascending colon, and the terminal portion of the ileum, Jackson's veil, Lane's band, etc., and which is primary, and which secondary it is difficult to determine. A careful analysis of our histories makes us believe that the appendix is more likely to be involved primarily than cecum or colon. Many bacteria must of necessity come to the lymph follicles of the appendix, and in a general ptosis of stomach and intestines, or a lymphatic hyperplasia we have potent factors for the development of a chronic inflammatory condition of this organ.

Splanchnoptosis of long duration may produce secondary fixation and displacement of stomach and intestines by the traction or constriction of adhesions, due either to chronic appendicitis, which, according to our observations, is peculiarly liable to occur in this condition, probably due to disturbances in the blood, nerve or lymph supply of the appendix, possibly to the pressure of stagnant

fecal matter, or to a chronic peritonitis of a very low grade, due directly to this stasis and the lack of tone of the intestinal wall, the migration of bacteria through this area of lowered resistance being the probable cause of a low grade of perityphlitis or pericolitis, which in turn leads to adhesions. It is especially interesting that the areas peculiarly susceptible to this circumscribed inflammation of low grade are the sigmoid, the cecum, the splenic, and the hepatic flexure. The liability of the gall-bladder being infected is, of course, the potent cause of adhesions about this viscus, while according to Hofbauer, the upright position reduces the motility of the gall-bladder and the flow of bile to a minimum, and favors stasis and retention, thus, of course, rendering infection especially likely to occur. This biliary stasis, according to Keith, is peculiarly likely to be met with in splanchnoptosis. In some of the cases old hemorrhages would seem to have been the cause of adhesions, while in still others the adhesions about pylorus or duodenum, originating from an ulcer or erosion in this locality, are probably metastatic in origin, as suggested by the clinical observations of Moynihan and the animal experiments of Peyer, the appendix being the most usual primary focus or are due to reflex disturbances of ennervation.

Symptomatology and Diagnosis. It would make the paper far too long if we entered into detail into the analysis of the cases as regards symptomatology, diagnosis, and treatment, and we shall, therefore, simply call attention to the most important points brought out by the thorough study of these 86 cases, especially of the 32 cases that came to operation in which our clinical findings could be compared with the exact conditions found by opening the abdomen.

In discussing the symptomatology of these conditions and the diagnosis from the clinical findings we shall touch upon the symptoms due to disturbances of the motor, secretory and sensory functions, obstructive symptoms, symptoms due to chronic inflammatory conditions, to constriction of nerves, to fecal stasis, symptoms of so-called auto-intoxication, symptoms referred to other portions of the digestive apparatus from that of the lesion, pain, while as regards diagnosis we will discuss: (1) The knowledge derived from the study of the clinical symptoms, (2) the study of

the temperature, (3) the study of the leukocytes, (4) of the gastric, intestinal, and pancreatic secretions, (5) methods of studying the motor functions of stomach and intestines, (6) the study of the stool, (7) the study of the urine, and (8) the study with the *x*-rays, both the photograph and the fluoroscope being employed in practically all our cases.

Clinical Symptoms. Our cases could be roughly divided into two groups as regards clinical symptoms, one where the symptoms were vague and indefinite, and the patient had been regarded usually as a neurasthenic, psychasthenic, or nervous dyspeptic, the other where the symptoms were definitely localized, usually at the seat of the trouble—pain, tenderness on palpation with nausea, vomiting, etc.—sometimes referred symptoms as in certain of our cases of chronic appendicitis where the symptoms were typical of a pyloric obstruction, or a gall-bladder attack, or a gastric ulcer, and as in certain cases of pericholecystitis where the symptoms were quite typical of achylia gastrica.

Several of our cases of chronic appendicitis had been treated as gastric ulcer, and yet at operation the stomach seemed normal; in one case, however, in which this viscus was opened a small eroded area was found in the prepyloric region with a small thrombosed bloodvessel in its centre, and this may be the cause of the gastric symptoms, including hematemesis, which is met with in certain of these cases.

A careful physical examination often reveals areas of increased muscular resistance, notably in the ileocecal and right hypochondriac regions, while an enlarged loop of bowel, filled with fecal matter, either fixed or easily rolled under the finger, is often met with, especially in the cecum, sigmoid, or ascending colon. This latter is a frequent phenomenon in these cases, in many of which severe constipation is a very striking feature. In certain of our cases, notably two, where operation showed adhesions extending from the gall-bladder or duodenum to the lesser curvature of the stomach, typical symptoms of marked obstruction were present, yet each was greatly relieved by the prone position, evidently due to the fact that these adhesions were taut in the former, relaxed in the latter position—a point of importance in the *x*-ray diagnosis,

as the photograph with the patient lying on the stomach may completely miss the condition, while the orthostatic, fluoroscopic image gives the diagnosis definitely.

Pain. The pain in these cases is very variable, in some none at all, in others vague, diffuse and indefinite, in others localized definitely at the seat of the trouble, in others referred elsewhere, possibly due to the traction of adhesions, or the pressure upon nerves; in some cases the pain came on in attacks of greater or less severity, this being especially usual in the cases where there was a true obstruction even though of slight extent.

In certain cases of chronic appendicitis a persistent right-sided menstrual pain was met with, while of peculiar interest is the abdominal pain apparently due to regressive changes in the omental or sigmoid fat, the granular or shotty condition of the fat being probably due directly to toxins absorbed from the intestine and not neutralized by the liver, or to consequent pancreatic changes, and the condition in all probability being analogous to *adiposis dolorosa*. In one of these three cases in which the condition was met several very painful subcutaneous fatty nodules were present.

Pain of severe nature simulating a true coxalgia was met with in several of our cases of chronic appendicitis, and in this same condition painful or sluggish urination in a number of cases.

Fever. We have found slight elevations of temperature of great diagnostic aid in certain of our cases—in nearly one-half, in fact, a careful observation of the four hourly temperature showed that, unknown to the patient, there were occasional slight rises—often to 100° F., this being especially frequent in the cases of chronic appendicitis. As a rule this tendency to slight elevation in temperature is increased by exercise, and sometimes by indiscretions in diet.

Obstructive phenomena were sometimes met with, more frequently in the stomach, less so in the intestines, although in this latter a mild degree of obstruction is the probable cause of the constipation, and possibly of the toxic symptoms so frequently met with in this group of cases.

In the stomach, of special interest were the cases with true obstructive phenomena secondary to a chronic appendicitis, appar-

ently due in most cases to a reflex spasm, but unquestionably in some to a superficial pyloric erosion, the pyloric spasm being secondary to this.

Another interesting group of cases was that where the obstruction was due to adhesions between gall-bladder and lesser curvature of stomach, where in the upright position the ptosed stomach and the fixation of that point at which the adhesions were attached brought about either a definite pyloric obstruction, or, more commonly, an hour-glass stomach.

Toxic Symptoms. When we speak of toxic symptoms in these cases we are unquestionably treading on debatable ground, and yet in the vast majority of high-grade displacements or fixation of the large intestine symptoms are met with only explicable on this basis. Certainly the *anlage* is there—the displaced, kinked intestine, deficient in tone and propulsive power, and the consequent stasis of fecal material to a greater or less extent, and yet constipation alone cannot account for these toxic symptoms, for that condition is frequently of very high grade with no appreciable toxemia. What is the cause then of these toxic symptoms? Is it a toxin normally present but in excess due to fecal stasis? Or due to this stasis have the liver and other portions of the protective mechanism become insufficient (possibly due to repeated mild anaphylactic reactions from proteid poisoning, as suggested by Longcope's recent work) and toxins normally destroyed by the liver allowed to get into the general circulation? Or is there a tendency in these cases for an overgrowth of certain forms of bacteria, notably those Gram-positive anaërobes, associated with proteolysis? Or is the toxemia due to the products of certain ferments in excessive amount or perverted, as suggested by the work of Whipple, Stone, and Bernheim?

In 9 of our 32 cases a low-grade, persistent toxemia, or acute outbreaks of a toxic nature were met with, and it is suggestive that in 3 of these 9, at the time of operation definite chronic inflammatory changes were found in the pancreas—a true chronic pancreatitis, while in one of these 3 a temporary glycosuria accompanied the toxic outbreak, which consisted of slight elevation of temperature, intense headache, nausea, and vomiting, marked depression, a

peculiarly sallow skin, and great difficulty in moving the bowels. It is in this group of cases that symptoms regarded by some as vagotony, by others as hyper- or parathyroidism are seen, the latter being of peculiar interest when we consider the close relationship undoubtedly existing between pancreas and thyroid.

Whether these toxins are derivatives of the amino acids, and bear such a relationship as cadaverin to lysin or putrescin to arginin, we cannot say, but it is very striking what slight changes are necessary to convert the normal bases into products of great toxicity, and it is certainly possible that these changes may be brought about by the gram-positive proteolytic bacteria found in the intestines. While many dietetists have gone, undoubtedly, too far in prohibiting proteid food, especially meats, in these cases of so-called auto-intoxication, nevertheless, in our two most marked cases observed over many months, the elimination of meat from the dietary was the only successful method of lessening materially the frequency and severity of the symptoms.

The fact that these toxic bases can experimentally be destroyed by bacteria which set free acid, such as the various forms of lactic acid bacteria, is the scientific justification for their employment in this group of cases.

The Study of the Gastric Contents. The gastric contents were examined in all of our 86 cases, and in practically all not only after the ordinary Ewald test meal, but also twelve hours after the Haussman meal of boiled rice. According to this observer rice retention under these conditions shows an organic obstruction at the pylorus. While we found the test to be positive in our cases of true pyloric obstruction due to adhesions, nevertheless, it was also positive in certain of our cases of chronic appendicitis, where at the time of operation no organic pyloric obstruction was to be made out. Whether this is due to a spasm of the pylorus produced reflexly by the diseased appendix, or whether a superficial erosion of the pyloric or duodenal mucous membrane, possibly originating metastatically from the diseased appendix is the cause of the pyloric spasm, is open to conjecture; the fact that in the one case with no outward sign of organic trouble in the stomach, but in which the stomach was opened, a definite prepyloric erosion was made

out shows that in some of the cases, at least, the latter is the cause.

Speaking generally in these conditions associated with evidences of a definite inflammatory nature, a moderate leukocytosis and slight elevations of temperature, notably chronic appendicitis and cholecystitis, and also in cases with evidences of duodenal ulcer there was a tendency toward hyperacidity, and also toward the presence of a certain amount of free hydrochloric acid in the fasting stomach, while in those cases without definite inflammatory symptoms, pericolonic adhesions, and adhesions from the gall-bladder to the stomach, active inflammation although the thick grumous bile suggests previous infection of that viscus, the tendency was toward subacidity, while a number of these cases showed achlorhydria and some a true achylia. Whether the achylia was primary, the adhesions secondary or the reverse could not be definitely determined.

In two of these cases in which a pylorectomy was done, a condition of *linitis plastica* was found. Both cases gave a typical ulcer history running over a number of months, and yet in each no ulcer was found, but a peculiar smooth, thinned condition of the pyloric mucous membrane. Whether this is to be regarded as a precarcinomatous condition, the result of a previous superficial ulceration, a congenital condition, due to regressive changes in the pyloric glands, or is luetic in nature, one could not determine. Certainly in our two cases the last seemed improbable, as nothing in the history of the case suggested such a possibliity.

In determining whether or no the achlorhydrias were true achylias the Edestin test for pepsin was employed, while the Wolff-Junghan's test for soluble proteid was used as an aid in drawing conclusions as to whether the achylia was of a benign or of a malignant nature.

Study of the Stool. The examination of the stool is of great importance in these cases, notably, in those persons with symptoms of auto-intoxication.

The finding of mucus is of help in diagnosticating a colitis, which is very common in these cases. The occult blood test should always be made, of course after several days of a meat-free dietary, and in all our cases where the operation showed an active ulcer or an

erosion a positive reaction was obtained; in those cases shown at operation to be chronic appendicitis when blood was found in the stool, the probable cause was an erosion of the mucous membrane of pylorus or duodenum, as shown in one of our cases. This case is illuminating in that it shows the part played in the etiology of gastric (or duodenal) ulcer by disease elsewhere in the abdominal cavity, notably, chronic appendicitis, and is in harmony with Moynihan's view that duodenal ulcer is probably a secondary manifestation of an infection usually having its origin within the abdomen. In all cases in which there was a suggestion of sigmoid adhesions, producing displacement or fixation or constriction, a sigmoidoscopic examination was made.

It is essential in all cases with intestinal or general toxic symptoms to make a careful microscopic examination of the stool; the finding of large amounts of undigested fat or meat after the Schmidt diet, when no diarrhea is present, is very suggestive of some disturbance of the pancreas, either of a functional nature, or due to a chronic pancreatitis or a neoplasm.

In two of our cases with marked toxic symptoms, and many and dense adhesions involving the entire right side of the abdominal cavity, careful quantitative studies of the pancreatic ferments in the stool, especially the diastase, made us sure that there was marked pancreatic disturbance, and in each case a high grade of chronic pancreatitis was found. It would seem probable that this had been brought about by the long action of these toxins upon this organ, and that some at least of the general symptoms met with in certain cases of so-called auto-intoxication are due to organic changes in the pancreas. In each of these cases there was noted at operation, also, a wide open pylorus and enlarged duodenum, in one case two inches in diameter, and Finney has suggested that this may be secondary to the changes in the pancreas mentioned above. Codman, however, explains this as a gastromesenteric ileus, an explanation hard to harmonize with the operative findings. In the case of these two cases of chronic pancreatitis, in the one associated with jaundice there was a most interesting condition of xanthoma multiplex, possibly due to an increase in cholesterol, as suggested by Politzer and Wile.

To determine the diastase in the feces we employed a modification of Wohlgemuth's method, for the trypsin Fuld's method, also modified somewhat.

The Urine. The examination of the urine has proved of some help in certain of our cases, disappointing in others.

Slight pain or difficulty on urination may be suggestive of a chronic appendicitis with adhesions extending to the urinary bladder, and this was present in a number of cases; a transitory albuminuria is not unusual in the toxic cases, especially during an acute exacerbation of the symptoms, while in two of our cases there was an associated pyelitis, in one case due to the colon, in the other to the proteus bacillus, which seemed to have their origin in a chronic appendicitis, a condition to which Hunner has called attention in a number of cases.

The persistence of a considerable amount of indican also seems significant of a certain amount of auto-intoxication, but our experience with the so-called functional liver tests as a gauge of the ability of the liver to function properly, especially as regards its antitoxic function, has not been satisfactory. We have tried the urobilinogen and urobilin tests, and tests after the administration of galactose and levulose, but the findings have not been definite enough to warrant us in drawing any conclusions. Perhaps the new test, phenol-tetra-chlorphthalein, employed by Rowntree, Hurwitz, and Bloomfield, may be more productive of results, but the chemical processes taking place in the liver are so multitudinous and so complex that it is hard to believe that any one test can give us a fair criterion as to its function. In a number of cases we studied the diastatic ferment in the urine quantitatively in the hope that it would furnish us with data of importance in diagnosing disturbances of pancreatic function, but the results were inconclusive, probably due to the fact that diastase is so widely distributed throughout the body; from our experiments probably we shall obtain data of far greater importance in this connection by a study of this and other ferments in the stool.

The Leukocytes. In certain cases we have derived a great deal of help from the study of the leukocytes.

As our normal in the adult we have taken 6500 per c.c., of which

72 per cent. should be neutrophiles, a result obtained by us a number of years ago in the study of 50 normal individuals. In these cases we have studied we have certainly demonstrated that a persistent increase—usually up to 10,000 to 13,000, often with an associated relative increase of the polymorphonuclear neutrophiles, is very significant of a chronic inflammatory process of low grade; in our series this has been met with in practically all the cases of chronic appendicitis, and in all cases of adhesions originating in the gall-bladder when careful temperature observations showed the presence of a slight fever, in other words, where there was probably a definite cholecystitis. On the other hand, in the case of adhesions arising from erosion or ulceration of the mucous membrane, or from a pericolitis secondary to fecal stasis and intestinal atony, we have found, as a rule, no increase of leukocytes.

The Study of the X-Ray Photographs and Fluoroscopy. Nothing has been of greater value to us in this work than the study of the *x*-ray photograph and the use of the fluoroscope, Dr. Baetjer having made photographs in the prone position of all our patients, we ourselves having examined them with the fluoroscope, usually in the upright position. By means of the former we obtain a permanent record of the displacement, and are able to study more carefully the finer details, while on the fluoroscopic screen we are able to see the effect of the upright position, the character of the peristaltic waves, the effect of deep abdominal respiratory movements on malposition and fixation—of paramount importance in determining the character of the adhesions, and the possibility of massage and other forms of mechanical treatment in lessening the fixation, kinking, or constriction as the case may be. In difficult cases we have repeated the fluoroscopic examination several times, as well as having a series of photographs taken, as a transient change of form may be deceptive, and only persistence in the abnormality is absolutely diagnostic. This is of special importance in the case of hour-glass stomach in the upright position, a condition which, according to Hertz, may be spastic, due to ulcer of the lesser curvature, appendicitis, or gall-stones, orthostatic, or that form met with in high grades of gastroptosis, and that due to adhesions between liver or gall-bladder and lesser curvature. Two examples

of the latter were met with in our series; of great interest because the photograph in the prone position did not show an hour-glass stomach nor was it easy to understand how the comparatively loose adhesions between gall-bladder and lesser curvature could cause the stormy symptoms of a marked obstructive nature of which the patient complained; the fluoroscope explained the case, for in the upright position these loose adhesions became taut bands producing almost complete obstruction at the point of their attachment to a congenitally ptosed stomach. Again, if one is suspicious that the hour-glass stomach is due to reflex spasm secondary to an ulcer of the lesser curvature, it is well to try the effect of a week of bland diet, preferably milk, to determine whether the spastic condition will not be materially lessened under the treatment.

Although the fluoroscope and *x*-ray photograph are of fundamental importance, nevertheless, if these means are not at our command, it is very interesting to see how by careful palpation, percussion, and inflation of stomach and intestines, these organs can be mapped out very satisfactorily, with, however, the finer details lacking.

It is useless to discuss which is of greater importance in diagnosis, the *x*-ray photograph or the fluoroscopic findings, each should be employed in every difficult case for one is complementary of the other, what one lacks the other will furnish, and from the use of both a very complete picture both as regards form and motor function will be obtained.

Whether the bismuth given modifies the picture is still undecided; according to Best and Cohnheim this substance materially slows the emptying of the stomach, and yet anyone who has watched the rapid emptying in duodenal ulcer, in achylia gastrica, or in adhesions about the duodenum secondary to ulcer must feel that this inhibiting effect must be very slight.

Certainly in the *x*-ray photograph and the fluoroscopic images we have two of our most valuable diagnostic aids, although as yet the study of normal and abnormal is not sufficiently complete to warrant us in building up an entirely new anatomy, physiology and pathology of the digestive tract as has been attempted by certain of the more enthusiastic radiologists.

Treatment. There are certain points in the prophylaxis and treatment of these conditions which warrant mention. As regards prophylaxis a point of real insistence is the better after-care of surgical patients upon whom an abdominal operation has been performed. Often in these cases the second state of the man is far worse than the first, for instead of a comparatively inoffensive appendix he has a tightly bound-down cecum or ascending colon with adhesions extending to bladder, hepatic flexure, pylorus, or gall-bladder. In all abdominal operations where there is a chance for adhesions to form, frequent change of position during the first days after the operation and deep abdominal massage as soon as it is safe and kept up for a considerable period of time should be insisted upon; by these means unquestionably both the number and the denseness of the adhesions may be materially diminished, if not altogether obviated.

In all cases of congenital splanchnoptosis every effort should be made to increase weight, improve muscle tone, enlarge the lower thoracic zone, and avoid constipation, the latter, of course, largely by exercise, diet, massage, etc., in other words, to do everything to lessen the chance of marked fecal stasis, which in time may cause pericolitis, perityphlitis, appendicitis, sigmoid adhesions, and other conditions which in time will lead to marked conditions of secondary displacement, fixation, kinking and constriction, and possibly auto-intoxication.

If such a condition has developed we always try the effect of posture, having the foot of the bed elevated, sometimes insisting upon a rest cure in this position, the wearing of a properly made bandage or corset, which, obviously, must always be applied with the patient in the elevated hip position, a diet devoted more to the strengthening of the musculature than the laying on of fat, though the latter is also desirable, certain exercises designed to strengthen the abdominal musculature, and, secondarily, in all probability, the smooth muscle of stomach and intestines as well, and, if possible, massage, and possibly in certain cases hyperextension. If the adhesions causing fixation or displacement are loose it is surprising what beneficial results can be obtained by these methods; it is peculiarly interesting to study these cases week by week with the

fluoroscope, and note the ascent of the ptosed stomach and colon, although obviously no permanent result can be expected if the adhesions are very dense and surgical interference should be employed in these cases. Were the abdomen a rigid box, posture, supports, massage, and exercises would prove of little avail, but with a flaccid abdominal wall it can easily be shown that by these means, if properly applied, very material improvement in the position and in the functioning of the stomach and intestine can be accomplished.

Diet plays a large part in the treatment of these cases, notably those in which constipation or symptoms of auto-intoxication are present to a marked extent. For the former obviously a coarser, more stimulating dietary with plenty of fruit acids, plenty of cellulose, often with some of the agar-agar preparations in addition; in the latter condition our first object is to determine what type of food is causing the major portion of the trouble, and to eliminate that from the dietary if possible—in certain cases meat is undoubtedly this factor, and its elimination is productive of great improvement—this was very striking in certain of our cases, while in others, on the other hand, the patient became generally weakened by such a dietary without being materially benefited as regards his special symptoms. Certainly the application of Combes' dietetic principles to all of these cases is unwarranted, but in certain selected cases the results are often brilliant.

Barring the use of alkalies in hyperacidity, acids in subacidity or achylia with the administration of the pancreatic ferments in those cases where careful study of the stools warrant us in diagnosing pancreatic insufficiency medicines play a small role in these conditions. Laxatives are sometimes necessary, and patients often find that the toxic symptoms can be materially lessened, and often an explosive attack aborted, by the prompt administration of a mercurial purge. The administration of mercury in small amounts over a long period of time undoubtedly helps certain of these cases, a method of treatment employed extensively in France and England. In certain of our cases of probable cholecystitis the administration of bile salts and urotropin seemed to have proved of distinct benefit.

Surgery is often necessary in these cases, and is always justifiable if other means have failed. Removal of a chronically diseased appendix, separation of adhesions, pyloroplasty, gastro-enterostomy, opening and draining the gall-bladder, and cecostomy have been the operations done in our series. The last, cecostomy, with irrigation of the large intestine over a long period of time, certainly offers a real hope in certain of the very marked cases of auto-intoxication associated with dense adhesions, marked kinking and constriction, and consequent fecal stasis of a high degree. With the proper after-care, of which we have spoken, to reduce to a minimum the possibility of the formation of new adhesions, the results of these operations have been in the main extremely successful, and many cases of confirmed invalidism relieved to a surprising degree. We have had no opportunity to study the effects of gastropexy, colopexy, sigmoidopexy, ileocolonic anastomosis, resection of the sigmoid or of the colon, but physiologically it would seem that an appendicostomy or cecostomy with subsequent irrigation were preferable to the last mentioned operation. The migration of the omentum to inflamed surfaces, while, of course, productive of great good in limiting infection, is sometimes the direct cause of intestinal obstruction as in one of our cases.

In all cases of chronic appendicitis with ulcer symptoms the stomach and duodenum should be investigated for superficial ulceration or erosion, while when the omental or sigmoid fat shows regressive changes, is granular and abnormal in appearance, the pancreas should always be examined.

Certain points of special interest brought out by the study of these cases are:

(*a*) The necessity of going into the past history most thoroughly to determine if possible the primary acute lesion, only possible, however, in a portion of the cases, as in some the condition underlying the formation of adhesions is fundamentally chronic from its incipiency.

(*b*) It is remarkable how marked a displacement or fixation of stomach or intestine, especially the latter, may be present with no or very slight local manifestations, yet in many cases some impairment in the general health.

(*c*) If there are evidences of a definite inflammatory process, slight fever, a moderate leukocytosis, etc., the gastric picture produced reflexly by this process in appendix, or gall-bladder, or intestine, as the case may be, has a tendency to be of the hyperasthenic type, *i. e.*, hyperacidity, hypersecretion, with some pyloric spasm, while if the adhesions are present in these localities with no evidence of present inflammation even of low grade, the tendency is toward the asthenic type of stomach—subacidity, achlorhydria, or achylia gastrica.

(*d*) In certain cases of adhesions between gall-bladder or liver, and lesser curvature of stomach we have the organic basis for the orthostatic type of hour-glass stomach with obstructive symptoms, especially marked in the upright and ameliorated in the prone position.

(*e*) Coxalgia is present in a number of cases of chronic appendicitis, and if persistent without signs of tuberculosis should make us suspect this as a cause.

(*f*) In addition to the *x*-ray photograph, a careful fluoroscopic study should be made in all cases, in the upright and prone position, and during forced abdominal respiration, as this is the most satisfactory means at our disposal to study the effect of the adhesions upon the motor function and the degree of the fixation.

(*g*) Chronic changes in the pancreas are met with in some of the cases of fixation or displacement, associated with toxic symptoms, and the consequent disturbances in pancreatic secretion unquestionably play a considerable role in the production of the digestive and nutritional disturbances met with in these cases. Of great interest also are the changes in omental or sigmoid fat, sometimes met with in these conditions, and occasionally associated with considerable pain.

(*h*) In all cases, in addition to the proper dietetic and medicinal measures, notably the limitation for a time at least of the animal proteid foods, and the administration of pancreatic extract in certain cases of marked stasis with severe toxic symptoms, we should try by posture, exercises, massage, and the wearing of a properly made abdominal support to determine whether a definite improvement is not possible. As a criterion for this besides the change in the

clinical picture, weight, appetite, condition of the bowels, capacity for work, etc., great help may be derived from periodic fluoroscopic examinations to determine whether the viscera are in better position, are functioning more satisfactorily, and whether the adhesions have become looser, lessening the degree of fixation, displacement, or kinking.

(*i*) If non-operative treatment has proved unsuccessful, recourse to surgery is justifiable—appendectomy, separation of adhesion, drainage of the gall-bladder, pyloroplasty, gastro-enterostomy, appendicostomy, or cecostomy, as the case may be. The last two operations are certainly justifiable, and promise a very fair chance of bringing about improvement in cases of high grade displacement, fixation and kinking of the large intestine associated with the picture of a chronic toxemia. After all these operations, and, in fact, after all operations within the abdominal cavity, however simple, proper after-care is absolutely essential to prevent the formation of new adhesions, and in the lack of this after-care the surgeons have been singularly negligent, as a rule, and have sometimes left behind a condition no less and often more serious than the condition for which they operated. Such after-treatment consists of very frequent change in position during the early days after the operation, by moving the patient from side to side, by alternately elevating the foot and the head of the bed, and, as soon as the condition of the wound warrants it, massage of increasing depth to be kept up a considerable period of time. That such measures are effective is shown not only by the subsequent clinical history of the patients, but also by fluoroscopic examinations or *x*-ray photographs made from time to time.

(*j*) As so many of these cases of acquired displacement or fixation of stomach and intestine are secondary to a congenital splanchnoptosis, prophylaxis is most important in those with such a predisposition, as shown by the characteristic body form, and should consist of exercises, massage, diet, etc., designed to improve the tone of the abdominal muscles, to increase the abdominal fat, and to enlarge the lower thoracic zone. Such prophylactic measures are of special importance in children with this tendency.

Conclusions. A consideration of these cases will bring out certain general facts.

1. A large group of cases usually considered of functional nature have in reality a true organic basis in a fixation and displacement of stomach or intestines. In many cases it is impossible to find any cause for the condition except a long-lasting stasis of intestinal contents, which seems under certain conditions to lead to chronic appendicitis, pericolitis, or perityphlitis with subsequent formation of adhesions; in other cases a careful analysis of the clinical history will bring out an acute attack, often in the far past, and usually regarded as of trifling nature, which in all probability was the beginning of the trouble, the first cause of the changes being in the gall-bladder, or duodenum, or pylorus, or appendix, cecum, colon, or sigmoid as the case may be.

2. A chronic appendicitis, pericolitis, inflammatory condition of the gall-bladder, a superficial erosion or ulceration of the mucous membrane of pylorus or duodenum, or a neoplasm may cause adhesions and associated fixation or displacement of stomach or intestines without definite local signs or symptoms in which a diagnosis is only possible by the use of all the diagnostic aids at our command, study of the temperature at rest and after exercise, of the leukocytes, of the contents of the stomach after the test supper and the test breakfast, of the urine and feces, the former to help us in a fragmentary way, it is true, in determining whether the liver is insufficient in its protective mechanism against poisons produced or found in the intestines, poisons which probably play a considerable role in the production of certain of the symptoms of the case, the latter especially for occult blood, undigested foodstuffs, and for quantitative estimation of the pancreatic ferments; of the character and localization of pain or soreness if present, pain down the right leg, or in the right hip being of special interest in diagnosing chronic appendicitis, and the use of the *x*-rays, both radiophotography and fluoroscopy being employed by us in all cases, the latter in our experience being of fundamental importance, as by its use we are able to study not only change in the position of stomach or intestines, but also the effect of deep abdominal inspirations and expirations, and of the change from upright to

prone position; in other words, fluoroscopy will tell us as nothing else—except a long series of radiographs—the effect upon the motor function of stomach or intestine of the fixation or displacement. By the employment of all these means a correct diagnosis can be made in the great majority of cases, if we may judge by the verification of the diagnosis in our group of cases by the operative findings.

3. In certain of these conditions we have without doubt the organic basis for various vague functional disturbances of digestion or for conditions regarded as neurasthenia, psychasthenia, or of a condition of health, in which the patient is neither sick nor well, but always below par. An organic digestive condition, even if of very low grade, may change a person of even normal nervous habitus into a neurasthenic if it acts over a sufficiently long period of time, and obviously upon a susceptible nervous system, the type so frequently met with in splanchnoptosis, in which secondary fixations or displacements are so common, the effect will be greater and more permanent. It would seem, therefore, that the diagnosis of neurasthenia, psychasthenia, or chronic nervous indigestion is only justifiable after the physician, by the use of all possible diagnostic means, has been able to definitely eliminate the possibility of an underlying organic basis, of which these acquired fixations and displacements of stomach and intestines play a considerable role.

4. We must not forget in the study of these cases that function is more important than form, physiology than morphology, and the assumption that a change in position in the intestine from horizontal to vertical will materially increase the difficulty of propulsion is contrary to the fact that for eons of years this has been taking place in certain portions of the intestinal tract with no apparent disturbance. It is lack of tone not displacement *per se* that is the cause of the trouble, although in the origin of this atonic condition, adhesions, displacement, kinking, and constriction may all play a part.

Can we reconstruct the underlying processes from the clinical picture presented? From our clinical studies verified in many cases by the operative findings, we believe this is possible in the great majority of cases.

DISCUSSION

Dr. R. C. Cabot: I have two cases in mind which bear on the thesis of this paper.

1. A case of marked enteroptosis was studied by *x*-rays and treated by a regime, belt, and posture. There was much improvement. Subsequently another *x*-ray study was made and the visceral condition was found unchanged.

2. While in London recently I observed some *x*-ray studies of healthy medical students, made for the purpose of determining the normal intra-abdominal stratus. One particularly healthy young man was found to have a stomach which descended to the level of the pubes.

I mention these cases so that we may be warned of the danger of allowing ourselves to be deceived by another therapeutic fad.

Dr. S. J. Meltzer: Those who regard human beings as only another species in the animal family find the reason for these visceral prolapses in the departure from the primary quadrupedal mode of locomotion.

Dr. Brown: The paper is based on cases of acquired ptosis only; the congenital cases were not considered at all. We studied cases presenting evidences of kinks, adhesions, infection, toxemia, etc.

In our cases we have by fluoroscopic study demonstrated distinct amelioration of the displacements of the viscera, and have not been guided by improvement of symptoms alone. Of course, we realize that with the removal of belts or bandages the ptoses will recur.

ON THE VALUE OF X-RAY EXAMINATIONS IN THE DIAGNOSIS OF ULCER OF THE STOMACH AND DUODENUM

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The diagnosis of ulcer of the stomach and duodenum is at times a most difficult problem. Not infrequently important symptoms are absent and the cases then become so atypical, that any additional aid in diagnosis must be looked forward to with great satisfaction. The *x*-ray has presented us with an important additional means of diagnosis in the study of this affection. While we do not believe that this method is as yet sufficiently well developed to be relied upon alone, yet we are confident that it often offers most valuable assistance as an aid in diagnosis of quite as much practical value as any of the important symptoms of the disease, and taken in connection with the other signs is of the greatest diagnostic help. We have selected from our 80 cases of peptic ulcers, in which *x*-ray examinations have been made, 20 for this report, including those only concerning which we could feel confident as to the correctness of the diagnosis. Of these there are 10 cases of duodenal and 10 cases of gastric ulcer. Three of these cases, V, XV, and VIII were operated on, and the diagnosis was thus confirmed. Three others, XII, XVIII, and XIX, had been operated on, and the ulcers revealed at the time of operation, but were not interfered with, while the remaining 14 presented such typical symptoms of ulcer, including the presence of blood in the stools, that the correctness of the diagnosis in these, too, remains undoubted.

The cases were first studied clinically, and then without any note being given as to the nature of the disorder, were sent for *x*-ray examinations. The two reports were then placed side by side and the clinical and *x*-ray diagnoses corresponded so closely in every instance as to make the results appear most striking.

The *x*-ray diagnosis of gastric ulcer and duodenal ulcer has engaged the attention of the röntgenologist ever since the production of high-power apparatus has made it possible for us to get practically instantaneous *x*-rays of the gastro-intestinal tract.

It is, however, only in the last two years that we are really beginning to observe results upon which some reliance may be placed. The old theory that there is a possibility of diagnosing ulcer by bismuth adhering to the raw surfaces is now practically abandoned, inasmuch as experience has taught us that this rarely happens because of the fact that the irritability of the raw surface produces hypermotility with violent contractions, so that it is almost impossible for the bismuth to adhere to the raw surfaces. At present we are relying more upon the functioning of the stomach and intestines than upon the actual demonstration of the ulcer. Curiously enough, the diagnosis of duodenal ulcer is much simpler than that of gastric ulcer. One can practically always rule out the presence of a duodenal ulcer, but one cannot always rule out the presence of gastric ulcer. The true line of distinction is the fact that in an irritating lesion of the stomach, such as an ulcer, the hypermotility produced by it causes a tonic contraction of the pylorus with consequent retention of gastric contents over a shorter or longer period, according to the situation of the ulcer, and also the deformity, that the lesion may produce. On the other hand, in a lesion of the duodenum, we have again a hypermotility not only of the duodenum, but of the stomach itself; but in this case we do not have the spastic condition of the pylorus, and consequently the hypermotility produces a rapid emptying of the stomach contents. For example, in our experience in simple ulcer of the duodenum, not complicated by adhesions, we find the stomach will invariably empty the greater part of its contents in from fifteen to twenty minutes and will be completely emptied in from forty minutes to an hour. In gastric ulcer we have just

the reverse. There will be the primary quick expulsion of contents and then the spastic condition of the pylorus appears, and we have a retention, varying anywhere from two to four hours, depending upon whether the lesion is a simple one or complicated by adhesions.

Let us take up the consideration of the duodenal ulcer. Our experience seems to show that there are certain characteristic features connected with this lesion, which are more or less present in all cases. We have decided hypermotility, yet the contractions are quite uniform, and there is no tendency toward hour-glass formation of the stomach. The pylorus is patulous, and the bismuth flows quite freely into the duodenum. The duodenum is in very active contraction, and in many of the uncomplicated cases we find that there is a vacant area in some portion of the duodenum, and this area will persist throughout the period of the examination. At times we may observe bismuth running along either side with the vacant area between the bismuth.

Whereas this has not been proved experimentally, yet we are inclined to believe that this vacant area is the seat of the ulcer, and owing to its raw surface and irregularity the bismuth does not adhere to it; consequently we have this area free, which for want of a better name we have termed "vacant area." In all of the cases we do not have this area free from bismuth, and we are inclined to believe that this fact is dependent entirely upon the condition that the surface of the ulcer presents at the time of the examination. In two of our cases (E. L. R. and J. P.) which have not been included in this report, in which there had been a fresh hemorrhage, within twenty-four hours previous to examination, we have found that it is extremely difficult to observe bismuth in the duodenum; the entire duodenum being in such a state of irritability with consequent hypermotility that the bismuth would be shot through the duodenum almost instantly. Then we have another class of cases with active symptoms where the ulcer was not of long duration, and yet apparently not complicated by adhesions. In these cases the vacant area occurred most frequently (Cases II, III, IV, VIII, XI, XII, XIII, XVII). In the third type of cases in which the ulcer was complicated by the

formation of adhesions, the vacant spot was practically absent. We can account for this by the fact that the adhesions probably lessen the hypermotility of the duodenum, and consequently the bismuth cannot be expelled so quickly from the raw surface. (Cases XII and XIX.)

The first two classes of cases are the most easily diagnosed. Care, however, must be taken not to confuse them with another condition in which we may have a rapid emptying of the stomach, namely, with hypochlorhydria (achylia gastrica). In this condition we have a patulous pylorus, so that the stomach contents flow through quickly and freely. This condition, however, is not characterized by the same active contraction as we usually have in the duodenal lesion.

Nothing but the clinical findings would differentiate these two points absolutely. The third type of cases, in which we have an old ulcer complicated by adhesions, is the most difficult to determine. Here the duodenum, and even the stomach, may be so tied up with adhesions as to interfere very seriously with the motility of these parts, but even in these cases we find that the stomach is making a determined effort to expel its contents, and shows all the evidences of hypermotility, and at the same time we do not see any bulging of the walls around the pylorus, such as is commonly seen when we have a true obstruction in that region. The duodenum is apt to show constrictions, at the seat of the lesion, and if the ulcer is still present we may or may not have a vacant area. The stomach contents as a whole are expelled more quickly than in a normal stomach. In the case of F. H. M., a male, aged sixty-one years, who presented many symptoms of duodenal ulcer, but had no blood in his stools, and who had a marked gastric and duodenal hypermotility, together with the vacant area in the duodenum, an ulcer was not noted at operation, though the duodenum was not opened; however, a band of adhesions was present connecting the duodenum with the gall-bladder.

Our general conclusions in reference to duodenal ulcer are these: There is excessive hypermotility of the stomach with rapid emptying of contents so that the greater portion of the stomach contents is emptied within the first half hour, the stomach

contraction being practically normal, and there is no evidence of hour-glass formation. There is hypermotility of the duodenum with formation of a vacant area which remains fixed in all the examinations. The presence of a duodenal ulcer in simple cases uncomplicated by adhesions, can practically always be determined.

In gastric ulcer we are dealing with a much more difficult question. Here the question of the normal motility of the stomach is still open to debate, as evidenced by the fact that various authorities have given from two to six hours as being a normal period for expulsion of the bismuth contents. At present it seems to us that the gastric ulcer can be diagnosed in certain situations only. From the *x*-ray standpoint we are able to see practically only one surface of the stomach and a portion of the greater and lesser curvatures. Should the ulcer be situated on the posterior surface of the stomach near the lesser curvature, it is not visible because the bismuth contents of the stomach completely obscures that side, consequently we are unable to see any alterations or irregularities of the peristaltic waves. It is only when the lesion is situated on the anterior surface of the stomach, and along the anterior surface of the lesser and greater curvature that we can come to any conclusion. If the lesion is on the lesser curvature, close to the pylorus, by making repeated examinations of the stomach we are able to see irregularities in the peristaltic waves due to the induration and partial fixation of the ulcer.

If the ulcer happens to be in the profile we might obtain an irregular area not covered with bismuth. Here again we have active contractions with primary rapid expulsion of contents so that we will almost invariably find the Bishop's cap filled. (We are speaking now, of course, of those ulcers which are not in the pylorus itself, and producing active obstruction.) We get an excessive irritation from the ulcer with a consequent hypermotility, and a spastic condition of the pylorus, so that for the time being there is practically no expulsion of contents. It is only when this spasticity relaxes that a portion of the bismuth is expelled. The act of expulsion, it seems, sets up in waves, and again we have a complete closure of the pylorus so that the expulsion instead of

being regular and rhythmical is decidedly spasmodic and in spurts. When the ulcer is situated just within the pylorus, we may have absolute retention over a period of several hours more than normal. And again when the bismuth is expelled it may come in two streams, appearing as if there were some obstruction with small apertures on either side. In these cases we have found that this vacant area in the pylorus is due to the ulcer, and the excessive irritability has almost diverted the stream to each side of it. In gastric ulcer, whatever its situation, we can always look for retention of contents. Notwithstanding the hypermotility of the stomach, we do not have a hypermotility with expulsion of contents, but on the contrary, retention.

In these lesions we frequently find a tendency to hour-glass formation, due to spasmodic contraction with all the stomach contents in both the upper and lower poles. This has never been observed in duodenal ulcer. (Cases I, IV, V, VII, IX, X, XIV, XV, XVI, XX.)

The diagnosis between gastric and duodenal ulcer from clinical signs alone is often very difficult, and many clinicians consider it impossible in many instances to differentiate between the two. The *x*-ray findings of the two conditions differ, however, so markedly that this method affords an almost positive means of differentiation.

Since we have taken up the positive phase of ulcer it is wise to draw some conclusions as to the negative finding. In the first place we believe that we can rule out positively the presence of a duodenal ulcer. If we observe that the stomach contents are not expelled promptly, and that the greater portion remains after the lapse of an hour, we can maintain confidently that the trouble is not in the duodenum. Even in the old chronic ulcer, with adhesions, the motility is so marked that it cannot be overlooked. The negative diagnosis of gastric ulcer is not so certain. So many complicating phases are present in these cases that the retention of bismuth in the stomach does not appear to have the same significance as the hypermotility in duodenal ulcer. As has been pointed out in gastric ulcer, we have a spastic retention. In simple atony and in prolapse we may have retention and

yet the spastic character of the retention is not present, nor is there any tendency toward the formation of an hour-glass stomach.

Another very important point, which our studies have brought out in connection with duodenal ulcers, is that in a rough way we can approximately determine the degree of healing of the ulcer. In duodenal ulcer, when the patient is given the rest treatment and placed upon the proper diet, all symptoms will gradually disappear, and the patient will become, comparatively speaking, well. This usually takes place in from four to five weeks. At the end of this time, however, if a second bismuth examination be made, we will usually find the same characteristic signs present as in the fresh ulcer, though the patient shows no symptoms whatever. In a series of cases of duodenal ulcer, that have been examined from three to five weeks after the absence of symptoms, we have practically found no change in the motility of the stomach. (Cases II and XVII.) The same hypermotility persists, indicating that there is still an irritating lesion present in the duodenum.

When these patients are given the ordinary diet their symptoms are apt to recur in a short time. If treatment, however, is continued longer our experience has demonstrated that as the ulcer continues to heal, the motility of the stomach returns to a more normal condition, and by making repeated observations over a long period of time we can observe by the *x*-ray examinations when the ulcer is healed (Case III). There can be no question but that this is one of the most important findings of this kind of work, inasmuch as until this method was employed there was absolutely no means of determining whether ulcers had healed or not. Our only means of determining this question has been by a return of symptoms, when the patient was placed upon an ordinary diet, and this simply means a relapse for the patient. By means of *x*-ray examinations made from time to time, we are thus enabled to determine the progress of healing.

Conclusions. From our studies of the twenty cases of peptic ulcer in which *x*-ray examinations were made, together with our experience with many other cases, we believe that we are justified in drawing the following conclusions.

1. The *x*-ray offers most valuable assistance, as an aid in the diagnosis of peptic ulcer, and although this method is not yet sufficiently well developed to be relied upon alone without entering into the clinical aspect of the disease, it is of the greatest diagnostic help in obscure cases.

2. In duodenal ulcer there is an excessive hypermotility of the stomach, with rapid evacuation of the contents, so that the greater portion of the gastric contents is emptied within the first half hour; there is hypermotility of the duodenum with formation, usually of a vacant area, which remains fixed in all of the examinations.

3. The diagnosis of gastric ulcer can only be made in certain situations; that is, when the lesion is situated on the anterior surface of the stomach, and along the anterior surface of the lesser and greater curvature. We have in this condition an excessive irritation from the ulcer, with a consequent hypermotility, and a spastic condition of the pylorus, so that for the time being there is practically no expulsion of the bismuth. It is only when the spasticity relaxes that a portion of the bismuth is expelled. In gastric ulcer, whatever its situation, we can always look for retention of contents. In certain instances there is a vacant area in the pylorus; there is frequently a tendency to hour-glass formation.

4. The *x*-ray affords an almost absolute means of differentiating between gastric and duodenal ulcer.

5. By means of the *x*-ray we can positively rule out the presence of a duodenal ulcer.

6. We can approximately determine the degree of healing of an ulcer, which cannot be as certainly determined in any other way.

We append a brief abstract of the histories of our cases:

Case I.—February 5, 1911. Gastric ulcer. C. G., female, aged sixty-one years. The patient has had symptoms of indigestion for two years, consisting of pain, pressure, and fulness after meals, and nausea but no vomiting. The symptoms are more marked after solid than with liquid foods; they have become more and more intense, until the patient now vomits large amounts of the undigested food; she has lost but a small amount of flesh, and the discomfort after meals has gradually become more aggravated. On examination peristaltic movements are visible, and

an extremely painful area in the epigastrium presents itself. There is no palpable mass in the abdomen; the gastric contents show a total acidity of 40, free hydrochloric acid is absent. There is an absence of lactic acid, and the Oppler-Boas bacilli; blood is, however, present. A retention meal was given at night, and the stomach washed the following morning, when a large quantity of the food remains was returned. Occult blood is observed in the stools. A diagnosis of gastric ulcer with obstruction was made (notwithstanding the absence of free hydrochloric acid), because of the character of pain after meals, the duration of the disease, and the slight loss of flesh.

An *x*-ray examination revealed a stomach situated high up with an extremely bulbous pylorus and definite retention due to obstruction was noted. The patient was operated on April 3, by Dr. J. M. T. Finney. A thickened pylorus with obstruction was revealed, together with multiple ulcers in this region. A pylorectomy was performed and the patient made an uneventful recovery from the operation.

Case II.—December 2, 1902. Duodenal ulcer. W. T., male, aged forty-seven years. The patient had had indigestion for several years with periods of complete remission, lasting several weeks to a month. The indigestion consists of pain in the epigastrium two hours after meals, which is relieved by food, as well as when in the recumbent position. This discomfort is less with liquids than with solid food. On examination an epigastric painful point is revealed. No other tender areas are observed. The gastric secretion presents a total acidity of 60, free hydrochloric acid, 60. Occult blood is present in the stools.

The *x*-ray examination presents an extreme gastric hypermotility with rapid expulsion, the stomach being completely empty in an hour and a half. In the duodenum there is a small vacant area, at which bismuth was found absent, though there was bismuth in front of it, and behind it ("vacant area").

Case III.—November 26, 1912. Duodenal ulcer. C. F. B., male, aged sixty-one years. This patient had numerous attacks of gastric pains, extending over periods of from two to three months for the past ten or twelve years. These pains would appear two hours after meals, and would be temporarily relieved by food, and by alkalies, and would also disappear when the patient is in the recumbent position. Tarry stools were present in one attack. The last attack has been present for about two months. The patient has lost 8 to 10 pounds in weight. A gastric analysis made during a former attack (four years ago) revealed a total acidity of 96, free hydrochloric acid, 78; occult blood is present in the stools.

An *x*-ray examination showed an extreme hypermotility of the stomach with an area in the duodenum uncovered with bismuth ("vacant aera"). On March 31, 1913, another *x*-ray examination was made. Hypermotility

is present but not to the same degree as in the previous examination. This would indicate that the ulcer is going on to a healing stage. It is not so active as in the previous examination.

Case IV.—December 27, 1912. Gastric ulcer. J. S., female, aged thirty years. Patient has been suffering acutely for the past three weeks with marked epigastric pain, passing into the back between the shoulder-blades.

The pain is most acute immediately after taking food, and very much more so after solid than liquid food. She is relieved in the recumbent position. There is frequently nausea, and occasionally vomiting. The patient has vomited small quantities of blood. The gastric contents present a total acidity of 54, free hydrochloric acid, 48; blood; a bit of necrotic tissue; the feces present occult blood.

An *x*-ray examination shows a somewhat bulbous pylorus, which at times appears in a state of extreme tonic contraction, the bismuth, however, going through very rapidly. From the state of tonic contraction and bulging of the stomach, there must be some inflammatory condition within the stomach just at the pyloric ring.

Case V.—September 20, 1912. Gastric ulcer. S. M. B., male, aged fifty-six years. (Case referred by Dr. Boyd, of Jacksonville, Fla.) The patient has been affected for a number of years with gastric disturbances with remissions for variable periods of time (from two weeks to a month). The attacks are characterized by pain coming on a short time after meals, *i. e.*, in from fifteen to thirty minutes; they are accompanied by nausea and occasionally by vomiting. Eructations of gas and acid eructations are frequent. The distress is increased on taking solid food, and is less on liquids; it is also lessened when the patient is in the recumbent position. On examination an epigastric painful area is manifested. The gastric contents present a total acidity of 74; free hydrochloric acid, 0.21 per cent.; occult blood is present in the stools.

The *x*-ray examination reveals a persistent absence of bismuth about the junction of the duodenum and pylorus (vacant spot), the motility of the stomach being markedly increased. Dr. Boyd operated on the patient on December 1, 1912, and found a pyloric ulcer evidently of long standing, and there was marked induration, and quite a puckered condition of the stomach wall at this site.

Case VI.—May 21, 1912. Duodenal ulcer. D. S., male, aged thirty years. The patient has had three distinct attacks of gastric disturbances of the same character. The first attack occurred three years ago, the second last year, and the present attack began a few weeks ago. Between the attacks the patient is perfectly well, and can partake of all kinds of food. The attacks begin with heart-burn, pressure, and uncomfortable sensation in the region of the stomach, which are soon followed by pain; the pain appears several hours after meals, and is relieved by food; the

pain is usually relieved when the patient is in the recumbent position, as well as by alkalies. The pain appears frequently at night, awakens the patient, but lasts only for a short time. On examination the patient presents a painful epigastric area. The gastric secretion shows a total acidity of 80, free hydrochloric acid, 0.21 per cent. There is occult blood in the stools.

The *x*-ray examination shows a marked gastric hypermotility, seven-eighths of the bismuth having been expelled from the stomach in forty-five minutes; there is also an area in the duodenum just in front of the pylorus, where no bismuth remained. In none of the plates would any bismuth adhere to this small rounded area, which was about the size of a five-cent piece, bismuth appearing on both sides of it ("vacant area"); there is in addition a decided hypermotility of that portion of the duodenum, bismuth passing through that area with unusual rapidity. With this hypermotility and with the vacant area in the duodenum the diagnosis of duodenal ulcer is confirmed. There is in addition a much dilated cecum, prolapse of the ascending and transverse colon, and all are firmly bound down to the cecum.

Case VII.—December 20, 1912. Gastric ulcer. J. W. P., female, aged forty-seven years. This patient was first affected with the digestive disturbance two years ago; at that time she complained of pain appearing two to four hours after meals, heart-burn, and acid eructations. The pain was relieved by the taking of food and by alkalies. There was no difference as to the production of the pain, in relation to the food, solid food causing as much pain as liquids. The pain always disappeared, however, in the recumbent position. An examination at that time revealed an epigastric painful area; gastric contents with a total acidity of 100; free hydrochloric acid, 54; and with occult blood present in the stools. A diagnosis of duodenal ulcer was made, and a Leube rest cure undertaken; the patient recovered entirely in the course of six weeks, and was able to partake of all foods without discomfort. On December 20, 1912, she again presented herself for treatment. For the past four weeks she again complained of gastric pain, appearing fifteen to thirty minutes after meals, with distress from gas, some eructations, nausea, vomiting of an acid secretion, and at times a brownish matter; great relief is experienced from vomiting as well as when the patient is in the recumbent position. An examination reveals an epigastric and dorsal painful area, a gastric contents with a total acidity of 84; free hydrochloric acid, 0.22 per cent., with blood; tarry stools are likewise observed. There is no evidence of peristaltic movements, and after a retention meal given at night, the stomach is found perfectly empty the following morning.

An *x*-ray examination reveals a long vertical stomach, the greater curvature lying well below the crest of the ilium. Active motility is present, but the pylorus is very irregular in shape, and the stomach around the

pylorus is bulged out, showing definitely that there is some obstructive condition at the pylorus itself. Notwithstanding the active motility of the stomach, a good portion of the bismuth is still left in the stomach at the end of two hours. The delay in expulsion is due to a great deal more than the extreme prolapse, and is in all probability due to an ulcer.

Case VIII.—January 11, 1913. Duodenal ulcer. C. G., male, aged thirty-four years. This patient had had attacks of indigestion for the past four years, lasting from two or three weeks to three or four months at a time. The attacks are all characterized by similar symptoms. He has been affected with the present attack for the past four months. The symptoms complained of consisted of pains in the region of the stomach, appearing four to five hours after meals, which are intense at times, and which are relieved by the ingestion of food, and also by soda bicarbonate. The patient is extremely constipated and has lost 15 pounds in weight. He complains of the acid eructations, but is not nauseated, and does not vomit. An examination of the patient reveals a painful area to the right of the medium line. The gastric contents show a total acidity of 88, free hydrochloric acid, 0.21 per cent.; occult blood is present in the stools.

The *x*-ray examination presents the stomach in a state of excessive hypermotility with rapid expulsion of the bismuth contents into the duodenum. Just outside of the pylorus and in the first portion of the duodenum there is a ragged area in which no bismuth is found ("vacant area"). This persists in several plates, and from this, together with the hypermotility of the stomach, we can say confidently that there is an ulcer in the duodenum causing this change.

Case IX.—January 8, 1913. Gastric ulcer. J. G., female, aged fifty years. The patient has been affected with the present condition for the past two years; at times entire relief is obtained for a period of from two to three weeks. The symptoms complained of are a burning sensation in the region of the stomach, pain soon after the ingestion of food, followed by nausea and frequently by vomiting. The pain is so increased on taking solid food, that the patient had almost entirely discontinued solids on her on accord, and is living on liquids. The quantities vomited are usually small in amount, and there has never been any evidence of food taken the day before in the vomitus. The symptoms have been markedly lessened since she has been on liquids; the patient finds great relief in the recumbent position. An examination of the abdomen reveals an epigastric painful area, exquisitely painful to pressure. The gastric contents present a total acidity of 70; free hydrochloric acid, 62; occult blood is present in the stools.

The *x*-ray examination presents a large stomach, the pylorus drawn well over to the right side, and lying rather high. The motility of the stomach is good, but the expulsion is poor, indicating the presence of some inflammatory condition in the stomach, causing retention. On

account of the abnormal position of the stomach well over to the right side one has to take into consideration adhesions, but from the position of the stomach, and the way it is functioning, we believe that we have an inflammatory condition of the pylorus in the form of an ulcer, producing retention with adhesions outside, holding the stomach in an abnormal position.

Case X.—January 7, 1913. Gastric ulcer. Rev. C. R., male, aged twenty-five years. The patient has been affected with indigestion for the past three months. His complaints consist of pain fifteen to thirty minutes after eating, followed by nausea and vomiting. His pain is entirely relieved by vomiting. He has much less difficulty with liquid food than with solids; he is much annoyed by heart-burn and acid eructations, and gas, and is markedly constipated. During the past three months he has frequently observed tarry stools. On examination a tender epigastric area is revealed exquisitely tender to pressure. His gastric contents present a total acidity of 56; free hydrochloric acid, 42. A retention meal given at night reveals the stomach empty when followed by lavage the next morning. There is occult blood in the stools. An *x*-ray examination presents a prolapsed and enlarged stomach, yet, notwithstanding this, this organ appears actively motile. Bismuth is expelled with some difficulty, so that there is some retention at the end of three hours. In all of the plates there is an irregular area to which bismuth does not adhere, just inside of the pylorus at the lesser curvature of the stomach. We are here dealing with a gastric ulcer situated at the lesser curvature just within the pylorus.

Case XI.—January 18, 1913. Duodenal ulcer. A. W. M., male, aged twenty-three years. The patient has had disturbances with his digestion for the past year. He has pain in his stomach, two hours after meals, which is temporarily relieved by food, as well as when he is in the recumbent position. He has less distress from liquids than from solid foods. The pain is very distressing at times, but can always be relieved by the ingestion of food, even the drinking of hot water relieves it. The patient has not had nausea or vomiting, but is very constipated; is nervous, and suffers with headaches. On examination an epigastric painful area is revealed, and a painful area in the back to the left of the spine at the level of the tenth dorsal vertebra. The gastric contents present a total acidity of 85, free hydrochloric acid, 0.22 per cent.; and blood. The stools show occult blood.

The *x*-ray examination reveals a marked gastric hypermotility with an irregular area in the duodenum, not coated with bismuth and which persists in all the plates ("vacant area").

Case XII.—January 25, 1913. Duodenal ulcer. J. H. D., male, aged thirty-nine years. The patient was operated on in May, 1912, for cholelithiasis, no gall-stones were found, but a chronically inflamed appendix

was removed. At this time the surgeon noted the presence of a partially healed duodenal ulcer. The patient recovered from the operation, and after three weeks was taken with his present disorder. The symptoms manifested were nausea, fainting attacks, and severe epigastric pains which lasted for a period of from ten days to two weeks, and would disappear for from one to four weeks, and would then recur. The pain appears from two to three hours after meals, and is relieved by food, and by the use of soda. On examination an epigastric painful area is revealed. The gastric contents present a total acidity of 72, free hydrochloric acid of 62. A retention meal given at night shows the stomach completely empty of food remains the following morning. Occult blood is present in the stools.

An *x*-ray examination shows a long tubular stomach, prolapsed, the pyloric end lying well over to the right side. There is a hypermotility of the stomach and duodenum, and a vacant area in the duodenum. There are in addition, adhesions around the region of the appendix involving the cecum, ascending and transverse colon, and the sigmoid. These produce sluggish motility, but there is no evidence of obstruction.

Case XIII.—January 2, 1913. Duodenal ulcer. M. S., female, aged sixty-five years. The patient has had indigestion off and on for four years; she was taken acutely ill with what was termed an ulcerated stomach, and vomited a large quantity of blood at that time. The present attack dates back one year. It is characterized by severe pain appearing two hours after eating, accompanied at times by nausea and occasionally by vomiting. Liquids seem to give less distress than solids. The pain is relieved by the ingestion of food, by the use of alkalies, and by the patient assuming the recumbent position. Eructations are present to a marked degree, and heartburn is quite frequent. Tarry stools have frequently been observed. On examination an epigastric painful area exquisitely tender to pressure is revealed, as well as a dorsal painful area to the left of the spinal column, and at the level of the tenth dorsal vertebra. The gastric contents show a total acidity of 75, free hydrochloric acid, 0.19 per cent.; occult blood is present in the stools.

The *x*-ray examination shows that practically all the abdominal organs are displaced, the position being very abnormal, due to Pott's disease, which is marked. There is, however, extreme hypermotility of the stomach, so that three-fourths of the contents are emptied in from five to twenty minutes, and in one hour and ten minutes the stomach is completely empty; one portion of the duodenum is rather bulbous, and just behind this bulbous position is an area free of bismuth ("vacant area"). This persisted in several plates so that there is every evidence that we have here an ulcer of the duodenum. The abnormal position of the duodenum and the stomach is entirely due to the Pott's disease, and not to adhesions.

Case XIV.—December 25, 1912. Pyloric ulcer. J. B., male, aged thirty-six years. The patient has had stomach disturbances for four years, with periods of freedom from distress lasting several months. The present attack dates back one month. It is characterized, as all of the former attacks have been, by the following symptoms: intense pain appearing soon after meals, less pain, however, from liquids than solids; the pain disappearing when the patient is in the recumbent position; at times there is nausea and occasionally vomiting, with marked relief of pain after vomiting. The patient suffers with acid eructations and heartburn; he has never vomited blood. On examination a marked epigastric painful area is revealed. The gastric secretions show a total acidity of 88, free hydrochloric acid, 22 per cent. On lavage of the stomach in the morning, following a retention meal given at night, the stomach is found completely empty of all food remains. Occult blood is present in the stools.

An *x*-ray examination reveals a cow-horn stomach, and a rather bulbous pylorus, the motility of the stomach being good, but the expulsion of contents slow. Just above the pylorus a number of plates show an irregular ragged area with practically no bismuth adherent "vacant area." This case is clearly one of ulcer at the pylorus.

Case XV.—January 1, 1913. Gastric ulcer. L. K., male, aged thirty-nine years. The patient had a stomach disorder similar to the present attack a number of years ago. He again complains during the past three months, though he has had periods of relief of short duration. He suffers with severe pain; usually about three hours after meals, though this is not constant, as many times the pain appears immediately after meals; nausea and vomiting are irregularly present, and pain is relieved after vomiting. There are acid eructations, but alkalies do not relieve the pains. The patient has less distress on liquid food, and is usually relieved when in the recumbent position. On examination a painful epigastric area is revealed, and no peristaltic movements are observed. The gastric contents present a total acidity of 58, free hydrochloric acid, 38 per cent. Food remains and blood are observed in the gastric contents on lavage of the stomach in the morning, a retention meal having been given the previous night.

The *x*-ray examination reveals a long, prolapsed stomach with a sawed-off pylorus; that is, no evidence of any pylorus can be made out. The pylorus is, however, not completely obstructed, as there is some expulsion of contents, though there is a great deal of retention, with consequent dilatation of the stomach. Contractions of the stomach are quite active, however, showing that the dilatation is not primary, but it is evidently secondary to some obstruction of the pylorus. This obstruction is more from within, and is probably due to an old ulcer with the formation of a great deal of scar tissue and contraction.

On January 16, 1913, the patient was operated on by Dr. J. M. T. Finney. An ulcer was found near the pylorus in the lesser curvature of the stomach; this ulcer was resected, and a pyloroplasty performed.

Case XVI.—January 2, 1913. Gastric ulcer. B. D. C., male, aged thirty years. The patient has been affected with indigestion for five years with periods of remission. Five years ago he was operated on for appendicitis for symptoms much the same as he has now. Four years ago his symptoms became much more aggravated, while training at Muldoon's. The symptoms finally abated after several months. Several attacks followed. The last attack began November 15, 1912, and the patient has been troubled ever since. He has now pain beginning in the epigastrium, and radiating toward the back, following soon after the ingestion of food; more so after solids than after liquids, and is usually relieved by the recumbent position, though at times the pains are severe at night. Eructations are present which are sometimes acid in character; there is nausea at times, but no vomiting. On examination an epigastric painful area is revealed. There is also a dorsal painful area in the back, to the left of the spine, at the level of the tenth dorsal vertebra. Slight peristaltic movements are visible. The gastric contents present a total acidity of 72, free hydrochloric acid, 0.19 per cent. There is occult blood in the stools. A small amount of food remains is obtained in the wash water, the morning following a retention meal given at night.

The *x*-ray examination shows a large stomach, the pyloric end being drawn well over to the right side, and apparently fixed in that position. The motility of the stomach is quite good, but notwithstanding this, at the end of two hours and a half, a great quantity of bismuth remains in the stomach. It appears evident that we were dealing with some true pyloric obstruction, as one cannot conceive of the shape of the pylorus and its position due to adhesions causing such complete obstruction, and consequently must assume that there is some inflammatory condition within the stomach, an ulcer, leading to this abnormality.

Case XVII.—January 2, 1913. Duodenal ulcer. D. G. K., male, aged fifty-one years. This patient has had an acid dyspepsia for years; he had been troubled with gas and with regurgitation of acid food. In May of 1912 he had some pain in the stomach, which appeared three hours after meals, and which was relieved by food, and by the use of soda. On this account he was forced to diet himself, and has had to refuse all indigestible foods. The pain continued, and he finally vomited a large quantity of blood. This was soon followed by the passage of tarry stools, An ulcer rest cure was undertaken, and the patient made a speedy recovery.

January 2, 1913. His pains have nearly, though not entirely, disappeared; heart-burn is still present, and there are eructations of acid material. A very slight epigastric tender area still persists. The gastric secretion

shows a total acidity of 72, free hydrochloric acid, 58 per cent. Occult blood is present in the stools.

An *x*-ray examination reveals a hypermotility of the stomach, as over three-fourths of the contents is expelled within three-quarters of an hour. In the first portion of the duodenum there is a small constricted area ("vacant spot"), and beyond that point a slight bulging. With this condition, it is evident that there is some inflammatory lesion of the duodenum in the form of an ulcer.

Case XVIII.—November 4, 1913. Duodenal ulcer. M. L., male, aged thirty-four years. The patient had slight digestive disturbance for some time prior to October 23, 1912, on which day he was suddenly taken with a most violent attack of pain in the abdomen, and was removed to a hospital, and the abdomen opened and a perforating duodenal ulcer was revealed; a rapid life-saving operation was performed, but the ulcer was not excised; three or four weeks later, when the patient was placed on nearly full diet, he was taken with pain, which began two or three hours after meals, and which was relieved by food. The pain has continued to the present time; he has in addition heart-burn, and at times, acid eructations. On examination an epigastric tender point is revealed, as well as a tender area in the back to the left of the spine, on the level with the twelfth dorsal vertebra. The gastric secretion presents a total acidity of 86, free hydrochloric acid, 0.21 per cent.; the stools contain occult blood.

The *x*-ray examination reveals a long-drawn-out stomach with the pylorus to the right side, rather bulbous in character, with some obstruction at that region with excessive hypermotility. These two facts are apparently contradictory, indicating that we are dealing with two conditions; adhesions involving the pylorus from an old operation and a duodenal ulcer.

Case XIX.—February 11, 1912. Duodenal ulcer. M. B., male, aged thirty-nine years. The digestive disturbance began in this patient in 1901, when he began to complain of severe pain two to four hours after meals, together with acid eructations, gas, and frequently of vomiting. The vomited matter consisted mainly of food, and was frequently bloody; the bowels were constipated, and often of a tarry appearance; alkalies relieved his symptoms temporarily, and relief was always afforded by the ingestion of food. Periods of relative comfort alternated with numerous attacks of the kind already described. Five years ago the patient had a sudden and violent attack of pain, and was operated on for a perforating duodenal ulcer; this was followed by a diffuse peritonitis; then double empyema, and four months later obstructive symptoms manifested themselves, and a posterior gastro-enterostomy was performed; the ulcer was observed covered over by some scar tissue, and surrounded by many adhesions. The patient was relieved, and was again operated on a little later for an incisional hernia, and the appendix was removed. For several

weeks the patient had been suffering with a recurrence of his former symptoms; pain appearing two or three hours after meals, which is relieved by food or by lavage. There are acid eructations, but nausea and vomiting are absent. On examination a slight epigastric painful area is revealed. The gastric secretion presents a total acidity of 71, free hydrochloric acid, 62 per cent.; occult blood is present in the stools.

The *x*-ray examination reveals the gastro-enterostomy opening free and patent; there are adhesions around the pylorus and duodenum, with increased motility of the duodenum.

Case XX.—February 27, 1913. Gastric ulcer. M. A., female, aged thirty years. The patient has complained of stomach trouble for fifteen years, with periods of rather severe gastric pain; she suffers with nausea, and rarely with vomiting. The pain appears after eating, and is greater with solid than with liquid food, and is relieved when the patient is in the recumbent position.

The gastric secretion shows a total acidity of 70, free hydrochloric acid, 0.42 per cent. The examination of the stools presents occult blood. On examination an epigastric painful area is observed.

An *x*-ray examination of the stomach reveals a prolapse. The stomach is of the fish-hook type. There is a delay in the expulsion of the stomach contents, which can be very easily accounted for by the prolapse, but, on the other hand, there is an eroded area ("vacant spot"), just at the lesser curvature, within the pylorus, which persists in all of the plates.

DISCUSSION

Dr. S. J. Meltzer: I would like to make several remarks:

1. Since Kussmaul first recommended large doses of bismuth for ulcer of the stomach, at autopsies bismuth could be found except in the ulcer.

2. How do the writers of the paper explain the clear areas around the ulcers?

3. In *x*-ray studies of the movements of the stomach and intestine, it has been regarded that the movements of the gut are actually seen; I would like to suggest that we do not see the movements of the organs, but the movements of the bismuth only.

A problem occurs to me which should appeal to every practitioner. Bismuth has always been considered as indicated wherever there is a diarrheal condition to stop peristalsis; twenty-five years ago we gave 5 grains and wondered if the dose was too much; now we give 2 or 3 drams at a dose. In some experimental cases we give to cats of 3 kilos 5 grams

of bismuth in order to see the peristaltic movements; if we should give it to a man of 60 kilos in that proportion, we would have to give about 100 grams; the problem is, When would he have his next movement?

Dr. M. H. Fussell: The thing we wish to do is to make a diagnosis of ulcer which will stand the test of operation. I have often enough been discomfited to wish to know how the results of the writers have been proved.

Dr. W. S. Thayer: If these results are upheld by later observations, and if the stomach really empties itself so early in cases of ulcer, of itself or of the duodenum, then it seems to me that this communication is a very important one.

Dr. S. Solis Cohen: In similar work done with Manges at the Jefferson Hospital, we have found this same hypermotility and the *x*-ray findings agreed with the clinical signs and in some cases with the operative findings.

Dr. Friedenwald: Some of our cases were confirmed by operations; many, of course, were not subjected to operation.

Dr. Baetjer: I do not wish to convey the idea that we believe that we can make an absolute diagnosis of gastric ulcer by *x*-ray examination. These cases have all been checked by careful clinical and, where possible, by operative observation.

In reply to Dr. Meltzer's remarks, one would expect an ulcer in a dead stomach to be covered with bismuth; but in a living stomach, which by *x*-ray observations retained bismuth for seventy-two hours, it was found at operation that while bismuth was in the stomach there was none on the ulcer nor on a considerable area around it. We have not definitely concluded that the "vacant area" seen in our plates is the site of the ulcer, but the idea has been confirmed in several cases of operation.

The bismuth suspension given in studies of this kind are very mobile, and I believe we are justified in regarding the shadows cast by bismuth-containing-viscera as representing the outline of the organs themselves.

TESTS FOR HEPATIC FUNCTION AND DISEASE UNDER EXPERIMENTAL CONDITIONS

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At this time we do not wish to discuss any of the liver functional tests proposed by earlier writers, but desire to call attention very briefly to three tests which may be of value in the study of pathological changes in the liver. We expect to publish in the near future the detailed work upon which this abstract is based. A very few cases or experiments will be cited as characteristic examples of any given condition.

Lipase can be shown to be present in the blood plasma or serum of normal animals or human beings in a pretty constant amount. The method is briefly as follows: Four tubes are prepared, each containing 1 c.c. plasma or serum diluted with 4 c.c. distilled water and 0.3 c.c. toluol to check bacterial activity. To two of the tubes is added 0.26 c.c. ethyl butyrate, the other two serving as controls. The tubes are shaken, corked, and placed in an incubator at 38° C. for eighteen to twenty-four hours. They are then cooled in iced water, three drops of azolitmin added and titrated in pairs to a neutral reaction, using one-tenth normal acid and alkali. The two control tubes usually show the blood alkalinity to this indicator to be 0.1 c.c. of one-tenth normal acid and the butyrate tubes show the acid production to be 0.1 to 0.2 c.c. above the neutral point. This means that the total *lipolytic activity* is 0.2 to 0.3 c.c.

one-tenth normal solution, that the lipase of the plasma has split up the ethyl butyrate to this extent. We may speak then of a *normal plasma lipase* as 0.2 to 0.3 c.c., always speaking in terms of tenth-normal acid.

We have found that injury of the liver by chloroform, phosphorus, hydrazine, etc., will always cause a rise in plasma lipase. After chloroform anesthesia of one to two hours, the plasma lipase in dogs will rise to 1 to 2 c.c. one-tenth normal acid. This rise takes place during the first few hours following the anesthesia, and usually persists during the second and third day following, when repair begins and the lipase falls to normal with recovery. If the animal or person is fatally poisoned the lipase will continue high until death on the fourth or fifth day. We have tested this lipase reaction in various experimental conditions where the liver is injured, and find a constant rise of two to eight times normal activity. We have followed the lipase in human cases and believe this test may be of value in certain groups of cases.

Eclampsia is variously defined, but if we limit the name to those cases showing peripheral hemorrhagic liver necrosis, this test is of the greatest value. We have had the opportunity of testing the blood from several cases in the service of Dr. J. W. Williams. In a recent case the blood was obtained during the first series of convulsions and showed 1 to 1.15 c.c. lipase, which pointed certainly to liver injury. The patient died the following day, with all characteristic symptoms, and the autopsy (3883) showed hemorrhagic portal liver necroses as usual. The plasma obtained shortly after death showed even higher liapse readings—1.1 to 1.4 c.c. In pernicious vomiting of pregnancy and uremia with convulsions, the lipase shows normal readings.

Jaundice may show a slight rise in lipase, but often a normal content, and obstructive jaundice of months' duration may show a low lipase. Pneumonia, peritonitis, leukemias, and various infections may show a rise in lipase to double normal or even more, but this will rarely confuse one. It is probable that in such conditions the excess of lipase is referable to liver changes—either liver injury or liver stimulation due to cell split-products circulating in the blood. *Yellow atrophy* of the liver surely will show a

high lipase reading, and in the *early* stages of liver cirrhosis the test will be of value and interest. *Liver cirrhosis* in the late stages may show a low lipase reading unless complicated with some liver necrosis.

Fibrinogen is normally present in blood plasma; in normal human beings it amounts to 0.3 to 0.4 gram per 100 c.c. of plasma. In dogs it fluctuates more widely, 0.2 to 0.5 gram. It has been shown in this laboratory[1] that fibrinogen may fluctuate with liver injury, falling to a low level at the time of injury and returning above normal during the repair which rapidly follows. It may drop to such a low level as to be the cause of hemorrhage or a hemorrhagic tendency, because the blood clots are too soft to check hemorrhage. This explains the hemorrhages of yellow atrophy of the liver, phosphorus, and chloroform poisoning, yellow fever, etc. In chronic liver cirrhosis the fibrinogen is often below normal and at times so low as to favor hemorrhage. In such conditions the fibrinogen estimation may give valuable information. When it falls to a low level it invariably indicates a grave condition and advanced liver injury, acute or chronic.

A rough estimation of the fibrinogen is possible by causing a little oxalate plasma to clot on adding calcium. The toughness of the clot indicates in a general way the amount of fibrinogen, and with some experience one can say whether the fibrinogen is much decreased in amount. The clear oxalate plasma may be heated at 59° C. for twenty minutes, the fibrinogen which is precipitated collected by centrifugalization, washed with cold and hot water, dried with alcohol, and washed with ether. This precipitate is then collected in a weighed Gooch crucible, dried at 120° C., and weighed. Twenty cubic centimeters are best used for each determination. This heat method is quite accurate except when the fibrinogen is very low; under these conditions it gives too low an amount, and if possible the plasma should be clotted with fresh serum and the fibrin weighed after washing, etc.

In certain cases of hepatic cirrhosis we have reported a very low fibrinogen index[2]—a drop to 0.05 gram or even lower. This

[1] Whipple and Hurwitz, Journal of Experimental Medicine, 1911, xiii, 136.
[2] Whipple, Archives of Internal Medicine, 1912, ix, 365.

is not an invariable finding in this disease, but when present is of the gravest prognostic import. In human cases of fatal late chloroform poisoning the fibrinogen during the last two days of the intoxication may drop to 0.048 gram and finally to 0.034 gram per 100 c.c. plasma (autospy 3726). When the liver is exposed to minor injuries it may respond with an overproduction of fibrinogen, which may rise even to 1 gram per 100 c.c. plasma. This minor injury may be looked upon as a stimulus, and the high fibrinogen content found in pneumonia, septicemia, peritonitis, etc., can be explained by the action of certain substances upon the liver epithelium. These substances may be derived from disintegration of the body cells or foreign cells, and when very abundant may be able to cause degeneration and even liver-cell necrosis, but in lesser amounts may be imagined to have a stimulating action (or irritative effect) upon the liver.

Phenoltetrachlorphthalein is a drug which is excreted by the liver into the bile. Abel and Rowntree[1] reported a study of this drug in connection with work on subcutaneous purgatives. Rowntree,[2] who was familiar with the characteristics of phtholtetrachlorphthalein and had established the normal excretion in dogs with biliary fistulæ, suggested that we use the drug in our work with abnormal hepatic conditions. The drug which was used has been supplied to Rowntree by Professor Orndorff, of Cornell University. A preliminary series of experiments with dogs whose livers had been acutely injured by various means, showed that there was a remarkable decrease in phthalein output during the period of liver injury. Rowntree, Hurwitz, and Bloomfield then proceeded to apply the test to patients in the wards, since which time the experimental and clinical work has been going on side by side with concordant findings. More careful experiments show that there is a very striking parallelism between the amount of liver injury and the output of phthalein. The drug was given subcutaneously in the first experiments, but it was found that the *intravenous* injection of the sodium salt offered many advantages over the oil method.

[1] Journal of Pharmacology and Experimental Therapeutics, 1909, i, 231.
[2] Journal of American Medical Association, January 29, 1910, liv, 344.

The procedure which gives best results in the experimental work may be outlined as follows: Females (dogs) are used when possible to facilitate catheterization, and are given 0.1 gram. phthalein when weighing between 10 and 20 pounds, 0.2 gram when over 20 pounds. The solution is injected intravenously, given usually in the forenoon. The dog is then given water (200 to 300 c.c.) by stomach tube to promote diuresis. After a period of five or six hours the urine is collected and a purge given, usually magnesium sulphate and croton oil in sufficient amounts to give several semifluid stools. The feces are collected the next morning, and experience shows that no phthalein can be obtained by subsequent purgation. It is important to obtain brisk purgation, as it is known (Abel and Rowntree) that the drug is absorbed from the large intestine and must be swept out rapidly to give a uniform result. Delay of purgation for twenty-four hours will drop the phthalein output from normal (40 to 50 per cent.) to 30 per cent. or even a little lower.

The method of extracting the feces is relatively simple and not time-consuming. The total feces are diluted to one or two liters as may be necessary in collection from the metabolism cages. The mixture is made alkaline with sodium hydroxide (5 to 10 c.c. of a 40 per cent. solution) and shaken until a good uniform mixture is obtained. One-tenth of this is taken and diluted to 500 c.c. with water, 3 to 4 c.c. of 40 per cent. sodium hydroxide added, and the mixture thoroughly shaken. Of this second solution are taken 100 c.c. for precipitation with basic lead acetate (5 c.c. of a saturated solution). After a few seconds a curdy precipitate comes down, and the solution is then made up to 200 c.c. with water containing 4 c.c. of sodium hydrate (40 per cent.). On standing the supernatant fluid shows a clear phthalein color and with filtration gives a solution which can be read directly in a colorimeter[1] against a standard solution, 10 mg. phthalein to the liter.

This procedure in our hands gives a very uniform phthalein output in the feces of normal dogs; 35 to 50 per cent. with 0.1 gram injections and 40 to 55 per cent. with 0.2 gram doses. The

[1] R. and G. modification of Autenreith-Konigsberger colorimeter, which reads directly in per cent.

same dog may show fluctuations within these limits, depending in part upon purgation and collection of feces. The drug given in these doses does not come through in the urine of a normal dog. Phthalein given by stomach and collected in the feces in the usual way will average 60 to 65 per cent., showing the amount of drug which is lost through contact with the intestinal mucosa and collection of the feces. When the phthalein is added to large amounts of feces it can be recovered completely (97 to 100 per cent.) by the method outlined above. This shows that only 10 to 15 per cent. phthalein is lost from the time the phthalein is injected intravenously until it is poured out by the liver in the bile into the duodenum. This indicates a remarkable degree of secretory activity and specificity of the liver epithelium.

When *liver injury* is produced by chloroform, phosphorus hydrazine, or other agents there is a drop in feces output to 20 per cent., 10 per cent., or even a mere trace, depending on the extent of the liver injury and the *phthalein* now comes out in the *urine* 0.5 to 4 per cent. The mechanism of liver repair is familiar, and with this return to normal the phthalein output comes slowly back to normal. This is illustrated by a single type experiment.

Dog 12–48. Strong female fox terrior, fourteen pounds.

April 3, 12 M. Phthalein, 0.1 gram intravenously. 5 P.M. Urine, phthalein negative, purged.

April 4, A.M. Feces collected; phthalein, 47 per cent.

April 8, 11 A.M. Chloroform anesthesia, one and three-fourth hours. At end of anesthesia given phthalein 0.1 gram intravenously. 5 P.M. Vomitus + urine; phthalein, 12 per cent.

April 9. No feces; dog vomits purges.

April, 10 A.M. Fluid feces; phthalein, 7 to 9 per cent. 12 M. Urine contains bile pigments; phthalein negative.

April 10, 3 P.M. Phthalein, 0.1 gram intravenously. 5 P.M. Urine, 100 c.c.; phthalein, 1.5 per cent. 7 P.M. Urine, 100 c.c.; phthalein, 1 per cent. 9 P.M. Urine + vomitus; phthalein, 1.5 per cent; purged.

April 11, 9 A.M. Urine + vomitus; phthalein, 2 per cent. 4 P.M. Abundant feces; phthalein, 25 per cent.

April 12. Dog is improving rapidly and eats well; twelve and one-half pounds.

April 15, 1 P.M. Phthalein, 0.1 gram intravenously. 4 P.M. Urine; phthalein, 0.1 per cent.; purged.

April 16, 10 A.M. Feces abundant; phthalein, 45 per cent.

The average amount of injury done to a dog's liver by two hours' chloroform anesthesia is a central necrosis involving about two-fifths of the parenchyma of each lobule. We may assume some such injury in the above case, and the prompt drop to less than half phthalein output with return to normal within a week is to be expected from the knowledge of the process of repair following such an injury.[1] It is possible to injure the liver so severely that the phthalein output may drop almost to zero, and in a majority of such cases the injury will lead to the death of the animal. The following experiment shows a severe liver injury followed by recovery, the phthalein falling almost to zero.

Dog 12–90. Small mongrel male, weight, eleven pounds.

April 10, 3 P.M. Phthalein, 0.1 gram intravenously.

April 11, 10 A.M. Feces abundant; phthalein, 43 per cent.

April 14. *Hydrazine* sulphate, 0.1 gram, given subcutaneously.

April 15, 1 P.M. Phthalein, 0.1 gram intravenously; hydrazine sulphate (second dose, 0.1 gram) subcutaneously; weight, ten pounds. 5 P.M. Urine; phthalein, 1.5 per cent.; vomits purges.

April 16, 9 A.M. No feces; vomits purges; dog looks very sick. Urine and vomitus; phthalein, 4 per cent. 4 P.M. Feces small amount; phthalein, mere trace (2± per cent.).

April 17. Jaundice is evident in skin; dog very dull. 11 A.M. One soft stool; phthalein, mere trace.

April 18, 10 A.M. Dog slightly better. Urine shows large amount of bile and faint cloud of albumin; weight, eight and one-half pounds. 2 P.M. Phthalein, 0.1 gram intravenously.

April 19, 9 A.M. Cage urine; phthalein, 2 per cent.; one fluid stool; phthalein, 8 per cent.

April 22, 12 M. Urine free from bile and albumin. Dog is very much better. Phthalein, 0.1 gram intravenously; weight, nine pounds. 5 P.M. Urine; phthalein, 2 per cent.; purged.

April 23, 10 A.M. Feces abundant; phthalein, 35 per cent.

It is obvious that this test can be of little value in obstructive jaundice, but it is interesting that little if any of the drug will escape in the urine. When the phthalein is given shortly after ligation of the common bile duct, the same or following day, the urine will show but a trace of phthalein. When the obstruc-

[1] Whipple and Sperry, Johns Hopkins Hospital Bulletin, 1909, xx, 278.

tion has been present days or weeks the phthalein will appear in the urine (1 to 2 per cent.), and we believe in each case this is dependent upon true liver injury. When the phthalein remains in contact with the body tissues for twenty-four to forty-eight hours in obstructive jaundice, it is changed to some substance which is not recognizable, but traces can be found in the gall-bladder three to six days after a phthalein injection in obstructive jaundice. The drug is not secreted by the intestinal mucosa, and in complete obstructive jaundice there is never a trace of phthalein in the feces.

Passive congestion of the liver cannot be produced in dogs to the extreme degree seen in human cases with broken cardiac compensation. However, it is possible to produce passive congestion of the abdominal viscera by means of stitches placed in the vena cava inferior just above the diaphragm, narrowing the lumen to 1 or 2 millimeters in diameter. Such animals develop extreme ascites, collateral circulation, enlarged spleen, etc., and they show a slight decrease in liver excretion of phthalein with no escape in the urine.

The Eck fistula produces a liver which has a scanty blood supply, chiefly arterial, and the liver undergoes a slow atrophy with some fatty change in the early stages. These dogs show a decrease in phthalein output (20 to 30 per cent.) and the urine contains 0.5 to 3 per cent. phthalein. This indicates a certain degree of liver insufficiency and liver injury. It is interesting that an Eck fistula dog living over a year has an output which has returned practically to normal, and only traces of phthalein in the urine, indicating that the liver has regained its functional balance. The clinical features of these animals support this interpretation.

It is clear that phenoltetrachlorphthalein gives promise as a functional liver test. It is excreted in the bile through activity of the liver epithelium, and not the bile-duct epithelium. Any agent which injures the liver parenchyma or interferes with its functional activity will cause a drop in phthalein output in the feces. Acute liver injury also is associated with an escape of phthalein in the urine, we believe, due to a modification of the phthalein through the agency of the injured liver cells, so that it

passes through the renal epithelium. Clinical material is being studied by Rowntree and his co-workers. The details of drug preparation, injection, and collection will appear shortly with a report on the clinical studies. It may be said that the findings in clinical cases which have been supported by autopsy or exploration are in harmony with the experimental observations. When it is possible to study the phthalein excretion, lipase, and fibrinogen, it is possible to get a good idea of the changes present in any given liver, and it seems certain that with accumulated experience we may be able to give more and more intelligent interpretation to the findings in these various tests.

DISCUSSION

DR. A. E. TAYLOR: Is it assumed that the liver is the sole source of lipase? If this fact is not established, on what authority in literature does Dr. Whipple base the assumption?

DR. WHIPPLE: It is obviously impossible to go into the literature of this subject in the discussion, or into the details of this work, which has covered four years. There are fluctuations of lipase observable after liver injuries, but no such fluctuations after injury of any other organ.

AN IMPROVED METHOD OF DILATING ESOPHAGEAL STRICTURES

By BERTRAM W. SIPPY, M.D.
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Stricture is by far the most common disorder of the esophagus requiring treatment. The conditions giving rise to esophageal stricture may be located extra-esophageal or intra-esophageal. Among the extra-esophageal conditions are aneurysm, mediastinal growths, pericardial and pleural exudates, disease of the vertebræ, extra-esophageal cicatrix, thyroid and thymus tumors, enlarged cervical glands, retropharyngeal growths, and swellings. The extra-esophageal causes are rare, however, compared with those located within the esophagus.

Intra-esophageal conditions causing stenosis are cicatricial narrowing, malignant tumor, chiefly cancer, spasm of the musculature of the esophagus, chiefly cardio-spasm, and diverticula.

Cicatricial narrowing arises most frequently from the ingestion of caustic acids and alkalies and corrosive substances of various kinds. It results rarely from other causes, such as ulceration occurring in the course of typhoid fever, peptic ulcer, the healing of ulceration due to impaction of foreign bodies, actinomycosis, syphilis, and tuberculosis of the esophagus.

The improved method that I shall describe is applicable to the dilatation of strictures of the common type; those due to cicatricial contraction, malignant disease, and other rare conditions giving rise to actual anatomical narrowing of the esophagus.

It is interesting to note that very early in the history of medicine one may find record of the use of esophageal sounds. They were used for the purpose of dislodging foreign bodies and pushing them on down into the stomach. Among the first instruments devised

were those made of wax; willow sprouts covered with intestine and onion stalks were also used in the same way. Evidence exists that the use of the bougie was soon extended to sounding and later to actually dilating strictured areas in the esophagus. In 1767, nearly one hundred and fifty years ago, Geuns devised an esophageal bougie similar in form to one that is in use to-day. The handle was made of whalebone, the bulb attached was made of ivory. Time will not permit me to even mention the various forms of esophageal sounds or bougies that have been in use. The bougies most popular to-day are the whalebone or steel rod type with olive bulbs attached, and the conical pointed gradually tapering flexible linen type.

Esophageal bougies are used to locate strictures, to aid in the diagnosis of their character, and when possible to dilate the stenosed areas so that food may reach the stomach through the natural passage. The difficulties and dangers attending the forcing of such instruments down the esophagus of a patient who is seeking relief because he is unable to swallow solid or liquid food becomes apparent on due reflection.

Cicatricial strictures arising from the swallowing of caustic acids and alkalies are often long, narrow, and tortuous. The whole length of the esophagus may be involved. Strictures due to cancer often involve the esophagus for a distance of four or five inches. The channel through the friable tissue of the cancerous growth is often tortuous. An ordinary rigid whalebone or steel rod bougie cannot be made to follow the windings of a long and very tortuous stricture. The bulb is usually arrested near the upper end of the strictured area. When dependence is placed on such bougies it very frequently becomes necessary to perform gastrostomy in order to prevent death from starvation. The flexible linen bougie was considered a decided improvement on the more rigid forms. Strictures that were impermeable to the rod type yielded readily to the flexible bougie.

It has been learned by experience, however, that it is necessary to employ great caution in their use. The small conical tip of the flexible bougie is trusted to enter the opening or channel leading into the stricture and in many cases to follow the windings of a

tortuous canal presenting irregularly projecting surfaces. In dilating carcinomatous strictures it is more or less confidently hoped that the point will go where it should, thread its way through the sloughing mass without perforating it, and guide the thicker dilating portion of the instrument safely through the stricture.

That the tip does follow the proper channel in such a large number of cases is more or less marvellous. Too many times, however, the point of the bougie engages on an irregularity of the cicatrized wall or penetrates a friable carcinoma and death results from esophageal perforation. It is obvious that there must be great danger in forcing any form of bougie through a strictured area in the esophagus without some means of guiding the point of the bougie.

To obviate this danger in former years it was my practice to pass a fine filiform whalebone or a fine wire bougie specially constructed through the stricture into the stomach. This was done with or without the aid of the esophagoscope. I used these filiform bougies or guides for specially constructed dilating bougies. I used this method very generally up to five or six years ago and fortunately always succeeded in accomplishing the desired dilatation without disastrous results. Although much more efficient and infinitely safer than the old method, some cases presented difficulties requiring great patience and not a little ingenuity. About this time I learned of the Dunham-Mixter method of using a silk thread as a guide through esophageal strictures. This method was seized upon as having in it great possibilities. Since then I have gradually elaborated an esophageal dilator or method of dilating esophageal strictures that would seem to embody the maximum efficiency and the minimum danger.

Because of the very greatly increased safety and efficiency of this method of dilating esophageal strictures I wish to earnestly urge the use of this or some similar method,[1] in all cases of organic stricture of the esophagus that admit of the use of any dilating instrument. The advantages are particularly striking when dealing

[1] See my article in the System of Therapeutics edited by Musser and Kelly, published in 1911. Dr. Plummer, of the Mayo Clinic has devised excellent methods by means of which the silk thread is used as a guide.

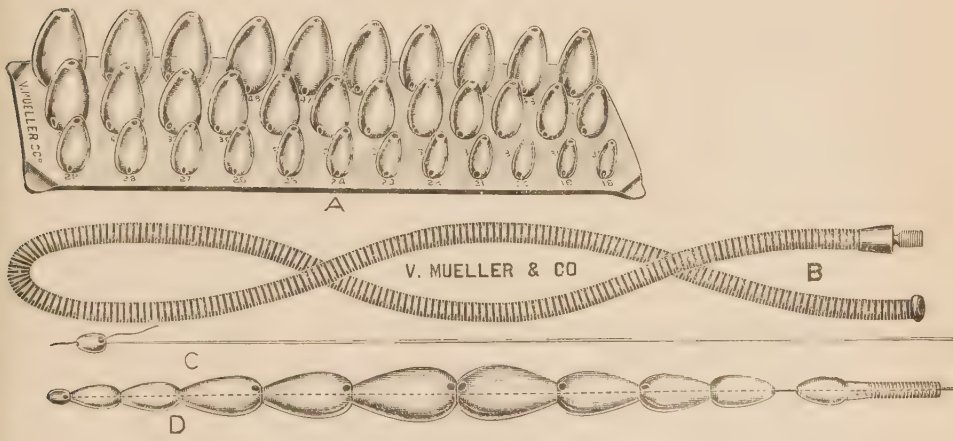
with tight and tortuous strictures whether due to cicatricial contraction or carcinoma.

The principle of using a silk thread as a guide is utilized in the following manner: A foot or more of ordinary silk twist, such as Belden or Corticelli, size D, is rolled up in a wad and swallowed. If necessary the wad may be placed in a capsule or incorporated in a piece of chocolate. The spool conveniently secured to the clothing by means of a safety pin is then slowly unwound so that three or four yards are swallowed during the first twenty-four hours. Subsequently from one to three yards may be swallowed each day. The taking of food or water facilitates the passage of the thread into the stomach. If the stricture is extremely tight only a small amount of water should be swallowed at one time. If the esophagus is overfilled, its contents, including the thread, are likely to be regurgitated.

A small twisted silk thread will eventually go through any stricture that will permit the passage of even a small quantity of water. After the silk reaches the stomach the normal peristalsis carries it onward. Usually at the end of twenty-four hours the thread that was first swallowed becomes sufficiently anchored in the intestine. It later passes out through the rectum. The thread is ready for use as soon as it is determined that it is securely anchored by pulling back on the end attached to the spool. In rare instances the stricture is so narrow or other mechanical conditions so peculiar that three or four days are consumed, before the thread is properly fixed in the intestinal tract.

The dilator (see illustration) consists of a series of graduated conical metal bulbs (*A*) that may be screwed on to a very flexible spiral introducer (*B*) twenty inches long made of piano wire, size No. 8. Each conical bulb is provided with a central canal that is continuous with the lumen of the spiral introducer when the bulb is adjusted. This canal is large enough to glide readily over the piano wire guide (*C*) The guide is four feet long, made of piano wire, size No. 20. A small perforated metal bulb, size No. 10 French scale, is firmly secured to one end of the wire by screw and solder. For a distance of eight inches adjacent to the bulb the wire is reduced in size to increase its flexibility.

The silk thread protruding from the mouth is first drawn back from the esophagus until it is moderately taut. The thread is then passed through the perforated bulb on the end of the piano wire guide. Holding the silk thread taut with one hand the wire guide is introduced into the esophagus with the other. The bulb follows the course of the thread and carries the wire safely through the stricture into the stomach. The lower end of the wire should be passed at least four or five inches beyond the lower end of the esophagus. If the thread is held firmly no harm can result even if the point enters the pylorus. The wire is easily held in position and serves as a firm guide for the conical bulbs used in dilating the stricture.



The diameter of the stricture is next determined by attaching conical bulbs one at a time to the spiral introducer and passing the bulb and introducer over the wire guide down through the stricture. Beginning with small sized bulbs, larger ones are substituted until one is found that passes through the strictured area snugly but without the use of force. A bulb slightly larger in diameter is selected with which to accomplish the first dilatation. The following procedure is advised:

A bulb several times smaller than the diameter of the stricture is first threaded point downward over the wire guide. From one

to three bulbs, each slightly larger than the one preceding, are then threaded to be followed by the dilating bulb. A similar cone of two or three bulbs is next threaded with points directed upward. The spiral introducer with a small-sized bulb attached is next threaded on the wire (see D, illustration). The operator then holds the end of the wire guide firmly in one hand; the detached bulbs sliding on the wire are then pushed down through the stricture by the spiral introducer. The first bulb being several times smaller than the diameter of the stricture enters the stricture without difficulty, opening the way for the slightly larger bulb immediately behind it. The next bulb being still larger prepares the way for the dilating bulb which enters the stricture in such a way as to exert an almost purely lateral or dilating pressure. All the bulbs are pushed through the stricture and into the stomach. The bulbs are drawn back through the stricture by means of the wire guide. As the guide is withdrawn the tiny bulbous point securely fastened at the lower end comes in contact with the lowest conical bulb which forces all the other bulbs backward through the stricture. The small bulb on the end of the introducer opens the way for the conical bulbs threaded with points upward. The stricture is thus gradually opened from below so that the dilating bulb enters the stricture both from above and below with the least possible traumatism to its walls.

This is an exceedingly important advantage in the management of carcinomatous strictures and even of greater importance in the treatment of the cicatricial type. The more a stricture is traumatized in dilating it the greater the inflammatory reaction and resulting connective-tissue formation. In using this method the pressure exerted in forcing the bougie through the stricture is applied in such a way as to act almost entirely as a dilating force, thus reducing traumatism to the minimum. The operator is enabled to judge with a great degree of accuracy the readiness with which the tissue of the stricture yields. Thus friability of the tissue with perhaps increased dangers or firm connective tissue requiring more force may be suggested. If thought best one or more larger sized dilating bulbs may be used in the same manner at each treatment. The rapidity with which a stricture may be

safely dilated is influenced by the character of the stricture, its length, the dilatability and friability of its tissue, and such factors as pain, hemorrhage, inflammatory reaction, and other conditions peculiar to the individual case.

After years of experience in esophageal work the writer has perfected and adopted this method of dilating organic esophageal strictures. When pressure is required one knows that the point of the dilator is directly in the channel of the stricture and that it cannot go astray. The sense of security experienced in applying the method is exceedingly gratifying. The danger of making a false passage by forcing an unguided bougie down the throat of a confiding patient is practically eliminated. The narrowest and most tortuous cicatricial strictures may be dilated and carcinomatous strictures may be treated with greatly increased safety and efficiency. In managing cicatricial stenosis of the esophagus it should practically never become necessary to perform gastrostomy for the purpose of feeding the patient, provided the stricture permits the passage of even a small quantity of water. The silk thread will go through practically any stricture permeable to water. After the thread is anchored in the intestine the piano wire guide may be made to follow the thread and appropriate sized bulbs may be crowded through the strictured area on the wire guide. The tissues of nearly all strictures will yield to the proper sized dilating bulb, hence with rare exceptions all strictures are dilatable by this method.

In selected cases, particularly if one has had considerable experience in esophageal work, a piano wire guide may be introduced without the aid of the silk thread. It is always much safer, however, to use the thread as a guide. A baby eighteen months old with an exceedingly tight stricture from swallowing lye was able to swallow the thread. In rare instances, however, the patient comes under observation at a time when, on account of the narrowness of the stricture, starvation is so far advanced that even the delay of a few days may be dangerous. An expert may be able to safely pass a fine filiform bougie or a hair-like wire, protected by a minute bulb on its lower end, and accomplish dilatation over such guides and thus spare the patient the inconvenience and danger of gastros-

tomy. In such cases I have used a set of smaller bulbs and a correspondingly small spiral introducer made of finer wire.

In all cases after the stricture has been dilated to the size desired, it is necessary to pass bulbs every few weeks, or months, or as often as experience with the individual case demands. Otherwise, the tendency is for the connective tissue to contract and narrow the opening.

Within the last few years many different plastic operations have been devised by means of which the attempt is made to construct an entirely new channel to take the place of the diseased or strictured esophagus. Dr. Paul Frangenheim has recently published a good resumé in *Ergebnisse der Chirurgie und Orthopädie*, 1913, Band v. Aside from the use of skin flaps and flaps from the wall of the stomach, portions of the jejunum, ileum, and colon have been converted into a false esophagus by embedding these structures beneath the skin, carrying them in some instances as high as the upper end of the sternum.

That surgeons today feel justified in devising and advocating such serious surgical procedures emphasizes the inefficiency of the older methods of treating esophageal strictures, methods that have been and still are in common use. The results to be obtained by the intelligent application of the simple method described in this article should be so uniformly satisfactory that such serious surgical operations should rarely, if ever, find justification. Likewise, the use of the esophagotome, Abbe string saw and retrograde dilatation of the esophagus through an abdominal opening into the stomach should scarcely, if ever, find justifiable indication.

DISCUSSION

Dr. H. S. Plummer: The case presented by Dr. Sippy and the details of the treatment are most interesting. I have used the general principles of this method in treating hour-glass stomachs; instead of using the series of graduated olives as Dr. Sippy does, I employed portions of two dilating bougies, cut through the point of greatest diameter and threaded on the

guide with their cut surfaces opposed, so that a spindle-shaped bougie resulted.

Dr. Mixter, of Boston, is the author of this method, but he has left the exploitation of it to Dr. Sippy and to myself.

Dr. S. J. Meltzer: It is very satisfactory to see such progress of therapy in these lines. Until a few months ago it was true that cancer of the esophagus was beyond the reach of surgical intervention. Within the past two months, in two cases carcinomas of the esophagus have been successfully removed.

Dr. Sippy: I heartily concur in Dr. Plummer's remarks as to the value of Dr. Mixter's work. Twenty years ago, Saunders fastened a piece of lead to a string and had a patient swallow it; but no attention was paid to the manœuvre.

I repeat again that wherever water will go, a string will go, wherever a string will go, a wire will go; and every stricture which will admit a string can be dilated. The string method surely avoids the danger of making a false passage.

THE INCIDENCE OF NEPHRITIS AFTER SCARLET FEVER

By JOHN McCRAE, M.D., M.R.C.P.
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The following observations are based upon rather more than 2100 cases of scarlet fever in the Alexandra Hospital, Montreal, all of whom have been treated in exactly the same way under my own supervision. Every patient has remained in bed twenty-one days from the onset of the disease, regardless of the severity of the attack, and has been restricted to a slender diet consisting of milk, water, cream, ice-cream, sugar, whey, junket, and some fruit juices; from the tenth day onward jelly is permitted. Drugs are never given when it is reasonable to withhold them.

Is there in scarlet fever a grave liability to nephritis? Of twenty-two authors of renown, nineteen answer affirmatively and three (the most recent) hold that the importance of nephritis has been much overestimated. Observations upon the present series indicate that a serious liability does exist.

The term nephritis is so variously interpreted that it is hopeless to attempt a deduction as to its incidence from literature. It has been stated by different authorities to occur in from 3 to 70 per cent. of all cases. For the purposes of this paper 1200 cases have been carefully analyzed, and when those ending fatally and those whose urinary history is deficient are excluded there yet remain 1034 cases, of which roughly 25 per cent. showed a disturbance of the urinary secretion subsequent to the febrile period. During the febrile period transient albuminuria, not to be confused with the foregoing, was observed in 15 per cent. of cases.

Of the 260 cases showing subsequent alteration, about 150

showed albuminuria at times, usually a trace on one or two occasions, always without casts. There remain 105 (or about 10 per cent.) which showed a more marked disturbance, half of these showing a moderate albuminuria and occasional casts. Finally, 5.5 per cent. of the entire number showed an actual change of sufficient severity or duration to be reasonably called nephritis. since 0.6 per cent. of the entire number had a history of previous nephritis, we may say that rather less than 5 per cent. of the total number of cases suffered nephritis, presumably as the result of scarlet fever. There was here no indiscretion of diet, no premature "getting up," and it is fair to assume that in a large number of cases of scarlet fever treated conservatively 5 (or 10 per cent. according to the strictness of nomenclature) suffered a renal lesion which may fairly be ascribed to the malady.

The above statement forms the discouraging part of the observations. On the contrary, in the entire 2100 cases a fatal result from nephritis has never occurred, with the exception of patients treated elsewhere and admitted late in the disease on account of nephritis that has developed; nor has a uremic convulsion occurred in the hospital in a patient treated thus from the onset. Edema is the exception, not the rule, nor does a severe dropsy among patients treated from the onset come to recollection; in four-fifths of the cases of well-marked nephritis referred to above, the diagnosis has depended entirely upon the urinary examinations. It is commonplace knowledge that fatal nephritis may follow a very light attack of the disease, but it seems a fair supposition that careless diet, improper activity, and lack of examination of the urine allow nephritis to progress so far that the renal lesion is severe before it is noticed.

The arbitrary rule of twenty-one days in bed and twenty-one days' milk diet was laid down at a time when the author had little experience of the disease, but the progress of time has brought no evidence which would lead him to change this treatment. It is true that text-books frequently recommend it; considering the difficulty of enforcing such rules in private practice, reasonable doubt may be entertained that so strict a procedure is widely accepted in actual practice.

If we consider the 106 cases of nephritis in all degrees, 20 showed some physical sign of the disease, whereas the others showed merely urinary change. Three grades of severity have been considered, thus:

Class 1.	Cases with physical signs, albuminuria, casts, etc.	20
	Cases with considerable albuminuria, casts or blood, or both, of which six had suffered from previous nephritis	37
Class 2.	Albuminuria (at intervals) and casts	3
	Albuminuria in small quantities for a long time and casts	17
Class 3.	Albuminuria in small amount, for a short time, with casts or at intervals with casts	30
	With these may also be mentioned cases of albuminuria without casts, usually only a trace	152

In 69 cases the time of onset of nephritis was as follows:

First week, 33; second week, 7; third week, 18; fourth week, 7; fifth week, 3, and later 1. Thus over 84 per cent. of these cases antedate the time of getting up and the time for free diet, and would be found in the routine urinary examination of the first three weeks.

SUMMARY. 1. In 1034 cases analyzed, urinary disturbance, subsequent to the fall of fever, arose in 25 per cent.

2. These cases were so strictly and so uniformly treated, that it seemed reasonable to blame the disease for the result.

3. Five and one-half per cent. of the cases showed definite nephritis, of whom a small number (0.6 per cent. of the whole) had previously suffered from the disease; other 5 per cent. showed signs which were milder, but which nevertheless might strictly be considered those of mild nephritis. There is a strong tendency to renal disease after scarlet fever.

4. Physical signs and symptoms of nephritis were seen in 20 cases (2 per cent. of the total number).

5. Fatal nephritis, severe dropsy, and uremic convulsions occurring in the first attack are probably nearly always the result of lack of care.

6. In 2100 cases treated from the onset, no deaths, no uremic convulsions, and no severe dropsy have occurred.

7. In 84 per cent. of the cases of urinary disturbance above quoted the signs or symptoms appeared in the first twenty-one days after onset of scarlet fever.

DISCUSSION

Dr. W. S. Thayer: I wish to ask, through how many years and in how many epidemics did Dr. McCrae's cases occur?

Dr. Jos. L. Miller: Which does Dr. McCrae regard as the most important conservative factor in his cases, the rest in bed or the diet?

Dr. McCrae: The cases were taken as they came in the Alexandra Hospital during seven years and in all epidemics.

I cannot say which is the more important, the rest in bed or the diet; I am inclined to favor the rest.

FURTHER STUDIES OF EXPERIMENTAL NEPHRITIS; SOME EFFECTS OF DIURETICS

By HENRY A. CHRISTIAN, M.D.
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(From the Department of the Theory and Practice of Physic, Medical School, Harvard University)

At several recent meetings of the Association of American Physicians I have reported the results of studies of experimental nephritis carried on in the laboratory of the Department of Theory and Practice of Physic at Harvard by myself and colleagues. During the past year, with the assistance of Drs. O'Hare, Walker, and Dawson, the effect of diuretic drugs in animals suffering from acute severe nephritis produced with uranium nitrate has been investigated and in some of these animals, with the coöperation of Professor Folin, variations in nitrogen retention have been followed. In the latter experiments the amount of non-proteid nitrogen and urea nitrogen in the blood has been determined by Dr. W. Denis in the laboratory of Biological Chemistry of Harvard University. The general results of these studies will be given here; the details of the different experiments will be found in several papers to be published later in the *Archives of Internal Medicine.*

In the series of experiments here reported only one animal, the rabbit, was used and only one type of nephritis produced, that following injections of uranium nitrate. A variety of drugs regarded generally as having a diuretic action was employed; not all of these, however, are considered to be diuretics in any constant sense of the word, and of some of them, such as spartein sulphate, there is much doubt that they should be considered to be diuretic drugs. These drugs were used, however, because they are often

employed by clinicians to produce diuresis. They were given to the rabbits twice a day in doses, with few exceptions, equivalent per kilo of body weight to those employed therapeutically in man.

A severe, usually quickly fatal nephritis was produced and the effect of the diuretic was measured by the length of life of the animals compared with control animals that had received the same dose of uranium nitrate; all animals were kept under the same conditions in large pens, with free access to water and a food supply of carrots and hay. The amount they ate and drank depended on their appetite, and varied much with variations in their condition. One hundred and thirty rabbits were used. In addition to these a number of normal rabbits received the same diuretic drugs over a longer period of time as controls to exclude any marked toxicity of the diuretic drugs.

It was found that diuretic drugs in rabbits with severe acute uranium nitrate nephritis had a detrimental effect in that they shortened the lives of the animals. With diuretin given by stomach tube (in some of these animals the doses were much larger than the usual therapeutic dose for man), rabbits with nephritis lived six days while controls lived 6.9 days. When the diuretin was given intravenously they lived four and one-fifth days while controls lived six and one-fourth days. With caffein, soluble theocin (theocin sodium acetate), potassium acetate and spartein sulphate given intravenously the average length of life was five, four and four-sevenths, four and four-sevenths, and six days respectively while controls lived eight and one-fifth days. As all the drugs were dissolved in water so that the dose per kilo of body weight was contained in 4 c.c. of sterile water, a considerable amount of water was introduced per diem intravenously in the rabbits. Hence, to determine any influence of the water in a small number of nephritic rabbits water alone was given intravenously. These lived an average of five and one-sixth days while of controls two survived and two lived an average of five days. In all experiments control rabbits were selected at random from stock pens at the same time the rabbits to receive diuretics were chosen.

In another series of twenty-one rabbits more accurate metabolism studies were made. These rabbits were kept in metabolism cages;

their food (oats and carrots) and water intake and urine output were measured. Their non-proteid and urea nitrogen in the blood and urinary nitrogen were determined by Dr. Denis as indicated in the introductory paragraph. The urine was collected in three-day periods to correspond with the determinations of blood nitrogen.

In normal rabbits diuretin given twice daily produced no distinct change in the three-day amounts of urine; the amounts showed no constant change and the variations were no greater than when no diuretin was given. The amount of non-proteid nitrogen and urea nitrogen in the blood did not fluctuate under the use of diuretin in normal rabbits. In rabbits with severe nephritis, diuretin sometimes increased and sometimes decreased the urine flow; the latter happened more often in the very severe types. Nitrogen retention in the blood usually steadily increased as the animals approached death; it could not be made out that diuretin influenced this rate of increase because the rate of increase varied as much in other rabbits without diuretin. While usually urine output steadily decreased, and nitrogen retention increased with the approach of death, occasionally urine output after decreasing to a small amount would increase, sometimes above normal, while nitrogen retention continued to increase. In these rabbits the rate of increase in nitrogen retention was not an indication of length of life; in one rabbit it reached a high figure (250 mgm. in 100 c.c. of blood as compared with the average normal of 35 mgm. in a rabbit) and the animal recovered. In another it reached a high figure and then began to decrease, although the animal died. In almost all of the rabbits, food and water intake fell rapidly as the rabbits sickened; urine output usually dropped faster than water intake; nitrogen retention in the blood increased; body weight fell markedly.

It is realized that the observations on metabolism in the last series are on too few animals to justify any generalization. The progressive rise in nitrogen retention, however, is of interest, and the failure of diuretin to influence it may prove of importance in a final evaluation of diuretic drugs in severe nephritis.

This particular set of experiments seems to justify the conclusion that in severe acute experimental nephritis of one type in the rabbit diuretic drugs are harmful when measured by their effect on

length of life; when tested by other means, such as measuring nitrogen retention in the blood, one of them (diuretin) does not appear to exert any favorable influence.

DISCUSSION

Dr. Jos. L. Miller: Dr. Christian stated that the amount of the diuretic drug given intravenously to his animals was equivalent per kilogram to the dose given to man; does he mean the dose for man by mouth? Was any difference noted as between the effects observed after mouth administration of the drug and after intravenous injection?

Dr. Solomon Solis Cohen: I do not think that Dr. Christian would have his results compared with the effects of these drugs in man. There is considerable difference between the acute toxic nephritis produced in the experimental animals and that which we have to deal with clinically under ordinary circumstances—especially the slow chronic forms but also the acute forms that complicate the infectious fevers. I should dislike to think that this valuable paper might cause the professional public to lose confidence in our long-tried and proved diuretic medicaments.

Dr. Christian: The dose by mouth in this work was given by stomach tube and varied from 0.014 to 0.4 gm.

The animals did vary much in the responses to the drugs; we found that stomach absorption was so variable in rabbits that we gave up that mode of administration and used intravenous injections exclusively.

Some German investigators have been using these drugs in comparable doses by intravenous injection in man with good therapeutic results.

As Dr. Solis Cohen intimated, we do not wish any therapeutic conclusions to be drawn from these experiments; they constitute only the beginning of a series to determine the therapeutic value of diuretic drugs, and we hope to extend the study to work in the wards.

BENZOL IN THE TREATMENT OF LEUKEMIA

By FRANK BILLINGS, M.D.
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Under this title the author reported (*Journal American Medical Association*, February 15, 1913, lx, 495 to 498) five patients suffering from leukemia.

Although but a short time has elapsed it seems best to report upon the results of the treatment in these patients and in others as conclusions may now be more definitely made. At the time the other report was made, attention was called to the cases reported by von Koranyi, who was the first to use the remedy in the treatment of leukemia. Attention was also called to the report of cases of purpura hemorrhagica due to benzol poisoning published in the Johns Hopkins Bulletin by Dr. L. Sellig, in 1910. Reference was made to the experiments by Santesson (Skandin, *Arch. f. Physiol.*, 1900, x, 7), who produced chronic poisoning with benzol with characteristic hemorrhages in pleura, lungs, and mucosa of stomach, hypoplastic bone-marrow and fatty degeneration of organs by the subcutaneous injection of benzol in rabbits and by wrapping the animals in cloths soaked in benzol.

G. Keralyfi was quoted (*Wien. klin. Woch.*, 1912, xxv, 1311), who had also treated seven patients with benzol with and without Röntgenotherapy.

So far as I know there have been no reports of patients so treated by others in the United States. By personal interview I have been told of the use of benzol in the treatment of leukemia in various places and with varying results. I have received letters from many physicians whose attention was called to the treatment by my report who have made the statement that they would begin the treatment of patients under their care with the drug. The results

in a few instances have been reported and have usually been ineffectual. The reason for the indifferent result has been, I think in some instances, due to the fact that the *patient has been permitted to be up and about, or the drug has been used in amounts too small to produce an effect.*

Since my article was published there have appeared various reports from abroad, one by von Stein (*Wien. klin. Woch.*, 1913, No. 49), by Tedesco (*Wien. klin. Woch.*, 1913, No. 2), by Wachtel (*Przeglad lekarski*, 1912, No. 52), and these reports have been almost uniformly in praise of the results of the treatment. Dr. S. Klein (*Wien. klin. Woch.*, March 10, 1913, No. 10) reports from Warsaw 22 patients suffering from leukemia treated with benzol. Of these 22 patients 3 were acute myelogenous leukemia, 1 subacute myelogenous leukemia, 14 chronic myelogenous leukemia, and 3 chronic lymphoid leukemia. Of the 22 patients, 10 had been under treatment for so short a time that the result was not stated.

Case 1. A man, aged fifty-four years, suffered from subacute myelogenous leukemia with moderate fever, rapid pulse, and large spleen. On August 29, 1912, red cells, 3,800,000; hemoglobin, 50 per cent.; leukocytes, 600,000; with a great number of myelocytes. From that time the patient received 5 grams of benzol daily in capsule. He suffered from severe eructations of gas and burning of the stomach and was obliged to stop the use of the drug for a few days. It was resumed on September 6 and 7, and then was discontinued. On September 10, 11, and 12, he received benzol by subcutaneous injection in the amount of 1.5 gram daily. The injection caused severe smarting and gangrenous infiltration. From September 13 to 18 he took 3 grams of benzol daily and from that time on to October 8, took from 2 to 3 grams daily either in capsules or in "*geloduratcapseln.*" He objected to taking the remedy because of the discomfort which it produced, and from October 8 it was omitted and he was given *x*-ray. The leukocyte count on September 17 was 408,000; on September 27, 502,000, and on October 7, when the remedy was omitted, 593,000. After two weeks of *x*-ray treatment the leukocytes diminished to 216,000. The spleen remained unchanged and enlarged. The patient lost in weight and strength with a gradually increasing anemia, with a red count of

2,500,000; hemoglobin 30 per cent., and died in a somnolent state on October 19, 1912.

The author states that this patient was difficult to manage because of the reluctance to take the benzol, and that it was given for only about twenty-seven days in an irregular way and in varying doses. The quotations are made in full from this patient because of the apparent difficulty in management and apparent worse condition which resulted while the drug was being used.

Case 2. A man, aged thirty-four years, suffering from chronic myelogenous leukemia with enlargement of the spleen. Leukocyte count, 400,800. Begun treatment on August 10, with 4 grams of benzol in capsules daily. Ten days later the spleen was very much smaller, the leukocytes, 292,000, and the patient left the clinic.

Case 3. A woman, aged twenty-two years, suffered from chronic myelogenous leukemia. Had borne a child nineteen months before. The lymph glands in the axillary region enlarged; spleen large; red cells, 4,800,000; hemoglobin, 70 per cent.; leukocytes, 250,000. Had *x*-ray treatment from November 19, 1911, until July 18, 1912, at which time the leukocytes were 19,250. She then took 4 grams of benzol daily until December 15, 1912, at which time the leukocytes were 12,440. Three weeks later without benzol the leukocytes were 9920. In the beginning of the benzol treatment the spleen was just palpable.

Case 4. A woman, aged thirty-six years, suffered from chronic myelogenous leukemia. For five months previously the patient had suffered from a left pyelitis. On October 3, 1911, a large and painful spleen was discovered. The patient showed red cells, 4,000,000; hemoglobin, 70 per cent.; leukocytes, 204,800. She received *x*-ray treatment from October 4, 1911, until January 9, 1912, at which time there were 84,600 leukocytes. On December 26, 1912, she received about 7 grams of benzol daily, with 142,800 leukocytes. On January 26, 1913, after seventeen subcutaneous injections of benzol of 1.5 grams the leukocytes were 153,200. February 4, after thirty-three injections of 1.5 grams of benzol, the leukocytes were 108,400, and on February 15, 1913, after forty-three benzol injections of 1.5 grams the leukocytes were 78,800. The patient became pregnant in March, 1912, and came to childbed

on November 18, a month too early. Child very small but living and well. The patient still remains under treatment.

Case 5. A woman, aged forty-five years, with chronic myelogenous leukemia who had suffered from cholelithiasis for two years. Recently she had noticed an enlargement in the left side of the belly. On examination both the spleen and liver found enlarged red cells, 3,800,000; hemoglobin, 58 per cent.; leukocytes, 973,800. On September 6, treatment with benzol was begun by subcutaneous injection, 1.5 gram daily. On September 13, benzol 0.5 gram, six times daily, and from September 19, seven grams daily. On September 24, 0.5 gram eight times daily; from October 8, 0.5 gram ten times daily; and from October 26, eight drops, ten times a day; from October 29, fifteen drops ten times a day, and from November 18, benzol omitted. During this period the original leukocyte count 972,800, diminished to 597,000, on October 3, with the larger dose by mouth the leukocytes increased to 750,400 and then until December 1, diminished very gradually to 340,000. The greatest fall in leukocytes was between October 16 and 26, when she was taking 5 grams of benzol a day by mouth.

Case 6. A widow, aged sixty years, suffering from chronic myelogenous leukemia. Seen in September, 1912, when she complained of pain in the belly, headache ringing in the ears, dizziness, difficult hearing, and had edema of the legs. She was anemic in appearance, enlargement of liver and spleen; red cells, 3,800,000; hemoglobin, 50 per cent.; leukocytes, 588,000. With benzol hypodermically 1 gram daily the leukocytes increased to 627,200. With benzol in capsules in the dose of 3 to 5 grams daily the leukocytes gradually diminished and on November 16 were 121,500. Then the benzol was increased to 300 drops a day until December 27, then 150 drops a day and on January 27 the leukocytes were 190,400. Then she received the benzol subcutaneously and from January 27, to February 9, in 23 injections she received 33 grams of benzol and the leukocyte count was 190,800. This patient was without treatment with *x*-ray. The statement is made that with the increase of leukocytes in the earlier part of the treatment there was no decrease in the size of the spleen or liver. Later in the treatment the liver and spleen returned almost to normal size.

Case 7. A man, aged forty-nine years, suffering from chronic myelogenous leukemia. Was seen on November 23, 1912. For two months he had been ill with fever, cough, loss of appetite and loss of weight. Three weeks before he was examined by Prof. Obrazcow in Kiew, who found a large spleen and diagnosed leukemia. He had suffered from furunculosis off and on for two years. At the time of the examination the spleen was enlarged and the right lobe of the liver easily palpated. The inguinal glands were visibly enlarged; red cells, 4,500,000; hemoglobin, 67 per cent.; leukocytes, 94,600. From December 23 until December 5 he received *x*-ray treatment. From December 14, benzol treatment was begun in the dose of 2.5 grams a day, gradually increased to 4.5 grams, which was continued until December 21. When *x*-ray treatment was omitted the white cells had fallen from 94,600 to 48,900, at which time the benzol treatment was begun, and when that was omitted they had fallen to 29,940. Two weeks later without benzol the white count was 4600 with practically a normal leukocytic formula.

Case 8. A widow, aged forty-five years, suffering from chronic myelogenous leukemia. On December 20, 1912, she complained of sweats, dizziness, poor appetite, and was pale. For six weeks she had noticed an enlargement of the belly and for the last few months had lost in weight. She had borne twelve children, the last three and a half years before. On examination she was poorly nourished, anemic, liver palpably enlarged and the spleen very much enlarged, reaching to the symphysis pubis; red cells, 3,800,000; hemoglobin, 46 per cent.; and leukocytes, 210,810. Immediately benzol treatment was begun in capsule with olive oil. In the first five weeks the white count varied gradually falling to 118,400. On the forty-third day the leukocytes were 113,000, four days later 69,000; then five days later an increase to 103,800. For a long time there was no change in the spleen. Then after six weeks it was markedly smaller. During fifty days of treatment of this patient she had benzol alone with undoubted improvement. General condition: spleen smaller and leukocytes reduced by 50 per cent.

Case 9. A man, aged thirty-six years, suffering from myelogenous leukemia. On November 18, 1912, patient visited dermatologic clinic for a priapismus, the first symptom and remained there until

December 22. On December 23, it was found that he had an enlarged spleen, palpable liver, slight enlargement of the inguinal glands, tenderness over the long bones of the legs, anesthesia of the skin of the legs, absent knee-jerks on the right side, red blood cells 3,800,000, hemoglobin 40 per cent., leukocytes 610,000. On December 24, benzol treatment was begun with twelve drops six times daily. On November 5, leukocytes had increased to 794,000, and on November 11 to 979,000. The benzol was increased to 15 drops ten times a day, and on January 16 the leukocytes were 565,000. He then received the benzol, 18 grams subcutaneously, until January 27, when the leukocytes were 68,000. After four days without the benzol the leukocytes were 11,520 and fifteen days later the leukocytes were 1720. This patient was treated with benzol alone with a marked result in the fall in number of leukocytes in the peripheral circulation from 979,000 to 1720. The benzol was given subcutaneously at one time because when taken by mouth it produced discomfort and vomiting. With the use of the benzol subcutaneously there was a more rapid fall of the leukocytes. The spleen was rapidly diminished in size. On February 1, about the time that the benzol treatment was omitted, it was noticed that the patient had very red lips, small, flat herpes, blister-like eruptions. A few days later the mucous membrane of the lips was exfoliated, leaving a rather hyperemic surface. Upon the anterior surface of the legs the palms of the hands and the soles of the feet there developed a light papular eruption which did not itch, but was very red. In the next four days this eruption was accompanied with an eruption of the skin of the whole body. At first the skin was livid and then became red brown. In the beginning the eyelids were swollen. After seven days with the exfoliation there was left a rather raw surface with a bloody, serous exudate. Seven days after the beginning of this eruption there were 11,520 leukocytes. After two weeks without benzol there were 1720, with hemoglobin 30 per cent. During the eruption of the skin the patient complained bitterly of the burning of the skin and had a fever of 39° C. The urine remained normal. The patient remains under observation. The author thinks the final result in this patient was due to intoxication from the benzol, and this is probably true.

He, however, took in a short period of time large amounts of benzol. The remaining three cases were lymphoid leukemia, all of whom responded rapidly to the benzol treatment.

Case 10. With a white cell count of 19,700 on October 16, received 5 grams of benzol daily in capsule, and on October 13 the leukocytes were 13,080, of which 33 per cent. were lymphocytes, 17.2 per cent. mononuclear cells, 49.2 per cent. polynuclears, 1.2 per cent. eosinophiles, 4 per cent. mast cells.

Case 11. A Rabbi, aged fifty years, showed on May 5, 1912, 2,800,000 red cells; hemoglobin, 58 per cent.; leukocytes, 120,000. He first received *x*-ray treatment from December 12, 1911, to August 13, 1912, at which time the leukocytes were 62,800; myelocytes, 86 per cent. He then received benzol from 3 to 3.5 grams daily until September 27, when the leukocytes were 3650; the lymphocytes, 67 per cent. Eight days without benzol the leukocytes were 13,800. Twenty-nine days without benzol were 11,800; forty days without benzol the leukocytes were 13,820. The benzol was given 5 grams daily until November 26, 1912, with leukocytes, 6400 (lymphocytes, 44 per cent.; polynuclears, 53 per cent.). This patient also suffered from tuberculosis and during this treatment the tuberculous process in the lungs seemed to increase, and finally there was a severe cough with bloody expectoration, increase of fever, and diarrhea.

Case 12. A laborer, aged thirty-five years, with lymphatic leukemia. In April, 1912, the patient had suffered from an itchy eruption of the legs, then swelling of the glands of the left inguinal region, then in the axillary region, then in the right inguinal region, then in the throat. He also suffered from gingivitis. For two weeks he had sweats. In December he had swelling of the belly. Was examined on January 13, and had taken benzol for six days from his own physician in the dose of 3 grams daily. On January 2, 1913, the red cells were 4,000,000; hemoglobin, 55 per cent.; leukocytes, 451,200 (lymphocytes, 78 per cent.). Both tonsils enlarged, especially the right. Enlargement of spleen to one hand's breadth below ribs. Patient took benzol in olive oil, 30 drops daily. On January 6 leukocytes were 604,000; January 11, 435,000. Patient left hospital on January 13, too early to come to any conclusion as to treatment.

It was noted that the leukocytes increased under the benzol from 451,000 to 604,000, an observation mentioned in many of the cases reported by others.

The main fact to be noted in the report of the twelve patients by Klein is that a fatal result occurred in a patient with subacute myeloid leukemia, who took the drug indifferently. One notes also the enormous dosage of the drug given both by mouth and subcutaneously in some instances, and especially in Case 9, where undoubted intoxication from benzol occurred. Another case was complicated with tuberculosis and apparently the tuberculous process was aggravated while the leukemia was very much improved. In the same number (*Wien. klin. Woch.*, March 10, 1913, xxvi, 365) S. Stern, of the University of Budapest, reports one case of myelogenous leukemia in a patient, aged fifty-two years, who showed enlargement of the spleen: red cells, 3,700,000; leukocytes, 264,000, of which 44.5 per cent. were myelocytes. Was given benzol in the dose of first 3 grams and then 6 grams a day in gelatin capsule and at the same time gave oil. Patient complained of burning in the stomach and later of some burning of the tongue and of sour eructations. Without the use of *x*-ray treatment the patient improved, the white blood picture falling from 264,000 on October 10, 1912, to 15,200 on January 7, 1913. During this time the red cells increased from 3,500,000 to 5,500,000. The myelocytes diminished from 44.5 per cent. to 3 per cent., while the polynuclears increased from 48 per cent. to 74 per cent. The spleen gradually grew smaller, and at the end of treatment was not palpable.

Since my report was made in February I have seen four other patients suffering with leukemia, two of the lymphoid and two of the myelogenous type. One of these, a man, aged forty-three years, a Rabbi, was admitted to the Presbyterian Hospital on April 10, 1913. Three weeks preceding this the patient consulted a specialist on account of deafness which came on rather suddenly and interfered with his preaching. The ear specialist found enlargement of the lymph glands on both sides of the neck and very much swollen tonsils and infiltration of the whole soft palate. In the following week the glands of the neck gradually

increased in size and caused considerable pain. Twelve days ago the patient first noticed enlargement of the axillary glands and then of the inguinal glands. The gland at the border of the right pectoralis major muscle also became enlarged to the size of an almond. The patient has had frequent nose-bleed for many years, bowels have been irregular, usually loose, for the last fifteen years. He has smoked cigarettes excessively. Physical examination showed a general glandular enlargement, with marked swellings in neck, axilla, groin, and belly. The spleen projects a hand's breadth below the costal edge and is firm and movable. The liver projects 13 cm. below the costal edge and is rather firm and sharp edged, not tender. Both faucial tonsils are enormously enlarged, almost touching in middle line, and the tissues of the soft palate and posterior pharynx are swollen, leaving but little space in the pharynx. The heart and lungs are negative. No evidence of enlargement of glands in the mediastinal space. Temperature, normal. Pulse ranges from 80 to 100. Weight, 127 pounds. Blood: reds, 3,310,000; hemoglobin, 45 per cent. (Dare); leukocytes, 48,500. Leukocytic formula: small lymphocytes, 81 per cent.; large mononuclears, 6 per cent.; indentate nucleus, 1 per cent.; polynuclear neutrophiles, 12 per cent. The patient was placed at the beginning upon 7 minims of benzol in capsule four times a day and with each dose was given a tablespoonful of olive oil. On April 16, the benzol was increased to 15 minims four times a day and has been continued in that dosage until now, May 1. The patient has not complained at all of any disturbance of the stomach in the use of the drug. In addition to the benzol treatment the patient had *x*-ray treatment over the spleen, liver, and glands varying the location of treatment each time, three times a week. On April 18, the leukocytes were 26,350, hemoglobin, 48 per cent. Leukocytic formula: small lymphocytes, 75 per cent.; mononuclear leukocytes, non-granular, 20 per cent.; polynuclears, 7 per cent.; polynuclear eosinophiles, 1 per cent. April 26, reds, 2,110,000; hemoglobin, 48 per cent.; leukocytes, 15,200. Twenty-four hour collection of urine showed nothing abnormal.

Through the kindness of Dr. B. W. Sippy I am able to report a patient suffering from chronic lymphoid leukemia. J. B., aged

forty-four years, a brickbaker, entered the Presbyterian Hospital on December 13, 1906. The patient had no recollections of any previous illness. In 1904, patient first noticed swelling on the right side of the neck. This was a single, rounded, movable, painless swelling. At the same time the stumps of tonsils which had been removed four years before were noticed to be much larger than the original tonsils. These stumps were removed. Since that time the swellings of the neck have continued to enlarge and other similar nodular swellings have appeared on the other side of the neck in the axillary regions and in the groins. General health has not apparently suffered excepting for a slight loss of weight. Patient has taken iodide of potash for a few weeks by advice of physicians. In examination of patient at that time the spleen was not palpable, but it was noted that the glands of the neck, axilla, and groins were painlessly enlarged. A blood count showed reds, 4,976,000; hemoglobin, 92 per cent.; leukocytes, 30,150. Leukocytic formula: small lymphocytes, 52 per cent.; non-granulated mononuclear cells, 11 per cent.; indentate nucleus, 5 per cent.; polynuclears, 32 per cent.; The patient did not remain in the hospital. Was given Fowler's solution when he left the hospital. He next entered the hospital on October 2, 1908, and reports that since his former visit has been under treatment with different physicians and in different places the greater part of the time, but does not know the nature of the treatment. For the first year there was little or no change in his condition, but during the last year the glands began to enlarge especially in the axilla and patient has not felt so well. During the last year he was given atoxyl, and following this the glands became smaller for a short period of time. Soon the glands increased in size very rapidly. During the last spring has been troubled with weakness and shortness of breath and the glands have become very much larger. Has had *x*-ray treatment during the last three months and has improved in regard to size of glands. During this period it was found that his spleen was palpable and it has continued to increase in size until now it produces a sense of dragging. In a general way the patient is weaker than formerly. An examination at this time shows large glands somewhat firm, not painful, in both sides of neck extending down to the clavicular regions. The glands

of axilla and groins are enlarged on both sides. The heart is normal. The lungs normal. Spleen is enlarged, passing to the median line in front and to the iliac crest below. Liver enlarged to hand's breadth below costal edge in mammary line. During his stay in the hospital the patient was given Fowler's solution in gradually increasing amounts and *x*-ray treatment every other day. Red cells, 5,000,000; hemoglobin, 83 per cent. (Dare); leukocytes, 153,250. Leukocytic formula: small lymphocytes, 92 per cent.; large nongranular mononuclears, 3 per cent.; polynuclears, 5 per cent. Under *x*-ray treatment and Fowler's solution in gradually increased dose, to the physiological limit, the leukocytes diminished to 72,800 on October 16, when the patient left the hospital. He reëntered the hospital November 18, 1910, suffering from a sore throat due to peritonsillar abscess. This time his red cells were 5,300,000; hemoglobin, 89 per cent. (Dare); leukocytes, 26,200. He left the hospital after three days and returned again on September 10, 1911. He reported that he had been feeling very well until a few days before, when a swelling developed in the side of the neck which rapidly enlarged and was painful, the pain was so severe as to keep him awake. At this time the physical examination showed enlargement of the lymph nodes in the neck from the submaxillary regions to the clavicles. Spleen palpably enlarged and somewhat hardened. Glands of groins and axilla moderately enlarged. Patient remained in hospital under *x*-ray treatment and on October 8, 1911, the leukocytes were 184,000; red cells, 5,120,000. On October 11, the leukocytes were 16,950, when the patient again left the hospital. On January 2, 1912, patient reëntered the hospital for *x*-ray treatment. He had now suffered from the disease so long that he was able to judge in an approximate way of the "need of *x*-ray," as he expressed it, and curiously enough was able to approximately name the number of leukocytes in a cm. of his blood. On January 4, 1913, the leukocytes were 68,000; hemoglobin, 75 per cent. On January 16, leukocytes, 29,600; on January 25, 21,700; on February 1, 15,700; on February 22, 9500; on March 3, 8000; on March 18, 7240; and on March 27, 8550. Patient reëntered hospital on April 8, 1913, presenting the same physical condition of former examinations. That is, enlargements of glands of neck,

axilla, groins, and spleen. April 7, leukocytes, 25,800; April 13, leukocytes, 10,555; hemoglobin, 70 per cent.; leukocytic formula, three hundred cells: small lymphocytes, 82 per cent.; large nongranulating mononuclears, 12 per cent.; indentate nucleus, 1; myeloleukocytes, 1 per cent., polymorphonuclears, 4 per cent. On April 16, leukocytes, 10,400; April 21, leukocytes, 10,060. Patient was given *x*-ray three days of each week and benzol 15 minims in capsule four times a day, taken with ginger ale. This treatment was begun on April 8, and the notable thing is the rapid fall of the leukocytes from 25,800 on April 7 to 10,550 on April 13, five days after beginning benzol treatment.

Of the patients formerly reported one is dead and four are still under observation. I feel that the subject deserves a complete rehearsal of the personal history of each of these patients.

Case I.—A. M. W., merchant, aged forty-two years, married, first examined September 29, 1910. Progressive loss in strength for past fourteen months, weight declined from 185 to 145 pounds. Patient weak and with very poor endurance. An irritating cough aggravated by variable weather. No expectoration. Profuse night sweats. Some fever with temperature of 100° to 101° F. at times. Dull ache and weight in left upper abdomen. Two weeks ago very severe pain in upper left abdomen aggravated by breathing. Health always good until present trouble. Appetite now good. Bowels regular.

Examinations. Is pale. General muscular apparatus flabby. Mucous membrane of throat and mouth pale. No lymph-node enlargements. Lungs and heart normal. Pulse rather rapid. Abdomen rather large, tumor in left upper abdomen corresponding to a much-enlarged spleen. Liver edge felt 3 cm. below costal edge at end of deep inspiration, not tender. Patient nervous and apprehensive; a fine tremor of fingers present. Urine: Specific gravity, 1018; contains no abnormal elements. Blood: Hemoglobin, 46 per cent. (Dare); reds, 4,200,000; whites, 352,000. Differentiation: Small lymphocytes, 10 per cent.; large lymphocytes, 6 per cent.; indentate nucleus, 2 per cent.; myelocytes, 10 per cent.; polynuclears, 70 per cent.; polynuclear eosinophiles, 2 per cent.

Treatment and Result. Patient was sent to the Presbyterian Hospital, where he received *x*-ray treatments and practically absolute rest in bed in a sunny room. Under this management there was rapid improvement in the patient's condition, a gain in weight, hemoglobin increased in percentage and the whites rapidly diminished in number. November 10, 1910, total leukocytes were 30,000; December 30 the total leukocytes were

7600 and showed 2 per cent. of myelocytes. The spleen diminished rapidly in size. Just before the holidays of 1910 the patient went to California, where he received *x*-ray treatments with some regularity, but was rather active physically and not quite satisfied with his surroundings. He returned within a month and the leukocyte count was 82,500 and the spleen palpable and projected from 3 to 5 cm. below the costal edge. Hemoglobin from 85 to 90 per cent. (Dare). Patient remained in Chicago, but not at the hospital, receiving regular *x*-ray treatments, and attended to some business affairs. His general nutrition remained good, but he was excessively nervous, the former nervousness apparently aggravated by a railroad accident which occurred on his way from California to Chicago. September 8, 1911, the red count and hemoglobin were practically normal; whites, 13,400; myelocytes, 20 per cent., of which 3 per cent. were eosinophiles; polynuclears, 66 per cent., of which 2 per cent. were eosinophiles; lymphocytes small, 10 per cent.; large, 6 per cent. During the remainder of 1911 the patient's condition remained about the same, the leukocytes never returning to normal count and myelocytes always present. The spleen remained just palpable. March 20, 1912, the leukocytes had increased to 100,000, of which about 10 per cent. were myelocytes. At about this time the patient was seized with a peculiar sensation in the lower chest and abdomen while taking a warm bath. He became very much frightened and collapsed. Following this there was some soreness over the spleen. The patient continued to receive *x*-ray treatments with some regularity, always with care as to the dosage, but on May 4, 1912, an *x*-ray burn of the skin over the spleen occurred, was painful and necrosis of skin occurred, leaving an ulcer about as large as the palm of an ordinary hand. This aggravated the patient's general nervousness and, of course, necessitated the withdrawal of the *x*-ray treatments. The ulcer was finally healed by a surgical plastic operation. During this period without *x*-ray treatments the leukocytes rose in number, reaching a total, October 12, of 191,000, of which there was always a considerable number of myelocytes. October 28, 1912, benzol medication was begun in the dose of 5 minims three times a day, and this was gradually increased so that by November 12 he was taking 15 minims four times a day. There was at first a slight rise in the number of leukocytes, and then after a few days a gradual diminution. November 21 the total leukocytes were 167,000. November 30 the whole blood-count was: reds, 4,100,000; hemoglobin, 68 per cent.; leukocytes; 133,000. December 12, reds, 4,100,000; hemoglobin, 75 per cent.; leukocytes, 18,250, and three days later the whites had fallen to 12,500; the small lymphocytes, 7 per cent.; large, 2 per cent.; indentate nucleus, 4 per cent.; polynuclears, 86 per cent., of which 6 per cent. were eosinophiles; myelocytes, 3 per cent. December 29, reds, 4,680,000; hemoglobin, 72 to 75 per cent.; leukocytes, 7500; small mononuclears, 18 per cent.; large mononuclears, 3 per cent.; polynuclears, 79 per cent.; myelocytes none. The benzol was stopped

December 22. January 7, 1913, reds, 4,960,000; hemoglobin, from 85 to 90 per cent.; leukocytes, 3600; small lymphocytes, 12 per cent.; large lymphocytes, 7 per cent.; indentate nucleus, 1 per cent.; polymorphonuclears, 80 per cent., of which 2 per cent. were eosinophiles and 3 per cent. basophiles.

As stated in the original article the condition of this patient deserves special relation because of the relapse after a phenomenal improvement under *x*-ray treatment. Then after the relapse ineffectual and final result from Röntgenotherapy, a severe *x*-ray burn.

On January 23, the patient had been without benzol since December 22. His red cells were 5,400,000; hemoglobin, 90 per cent.; leukocytes, 10,500; of which 56 per cent. were polynuclears, 5 per cent. polynuclear eosinophiles, 10 per cent. small lymphocytes, 5 per cent. indentate nucleus, 8 per cent., myelocytes, 5 per cent. myelocyte eosinophiles, and 10 per cent. mononuclear basophiles; unclassified, 1 per cent.

This leukocytic formula is one which would not be agreed to by probably any other individual who would attempt to differentiate the white cells because the blood picture is so different from that of the blood of an ordinary leukemia. Many of the leukocytes differ so from the ordinary types that they are difficult to classify.

On January 30 the leukocytes were 24,000, and benzol in the dose of 15 minims four times a day was again begun. On February 11, 28,000; on February 22, 50,000; March 3, 28,000; March 6, 29,000; March 10, 19,500; March 13, 15,000; March 29, 8400; April 10, reds, 4,190,000; hemoglobin, 83 per cent. (Dare); leukocytes, 10,200. Leukocytic formula: polynuclears, 67 per cent.; polynuclear eosinophiles, 8 per cent.; small lymphocytes, 2 per cent.; large mononuclear cells, 3 per cent.; transitional cells, 3 per cent.; myelocytes, 3 per cent.; eosinophile myelocytes, 1 per cent.; and basophile myelocytes, 13 per cent. April 18, the 15 minim dose was reduced to three times per day. Hemoglobin, 80 per cent.; leukocytes, 9250. April 24, hemoglobin, 95 per cent.; leukocytes, 7800. April 29, red cells, 4,880,000; hemoglobin, 83 per cent.; leukocytes, 14,000. Leukocytic formula: polynuclears, 74 per cent.; small lymphocytes, 5 per cent.; large mononuclears, 4 per cent.; indentate nucleus, 4 per cent.; myelocytes, 1 per cent.; polynuclear eosinophiles, 2 per cent.; basophiles, 10 per cent.

This patient gained in weight and strength while under this treatment and has not suffered from any disturbance of the digestive tract while taking benzol. He is intelligent enough to understand the gravity of the disease from which he suffers. His nervous balance fluctuates with the rise and fall of the leukemia. His spleen is not palpable. He is up and about and while not engaged in business is fairly active. He will continue under observation for an indefinite period and the dosage of benzol will be modified to meet the conditions found from time to time.

Case II.—J. G., druggist, aged thirty-six years, married, presented himself for examination, April 23, 1912. Weakness which began about ten months before had gradually increased. There had been a loss of weight from 166 to 150 pounds. Fulness and dragging in upper left abdomen had been noticed for six or eight months and recognized as large spleen three months before patient was seen. Some edema of feet had existed during the last few days, and night sweats at times. Aching pains in the long bones and sternum were noticed a year ago. Appetite was variable, and digestion good. Patient slept well. He had had the deep intramuscular injection of iron and arsenic and six or seven *x*-ray treatments over spleen during last few months. He had always had good health. One niece suffers from pseudoleukemia. Patient has good habits. He gave the following counts as made before coming to Chicago: March 6, 1912, hemoglobin, 30 per cent.; reds, 3,280,000; whites, 552,000. At a later time in March, hemoglobin, 40 per cent.; reds, 3,750,000; whites, 575,000. April 23, hemoglobin, 40 per cent.; reds, 3,500,000; whites, 415,000.

Examination. Appearance pale. Mucous membrane of mouth and throat pale. Tonsils slightly enlarged. No enlargements of lymph nodes. Spleen enormously enlarged, with lower border resting on crest of ilium, the right border extending beyond the median line. Urine: Specific gravity, 1.015; acid, no albumin, sugar or casts. Liver easily palpable, slightly tender. Sexual organs negative.

Blood Examination: Hemoglobin, 40 per cent. (Dare); reds, 3,500,000; whites, 578,000; differentiation: polynuclears, 44 per cent., of which 6 per cent. were eosinophiles; small lymphocytes, 18 per cent.; large lymphocytes, 6 per cent.; myelocytes, 32 per cent., of which a very large percentage were eosinophiles.

Treatment and Result. Patient was sent to the Presbyterian Hospital, where he has remained, receiving *x*-ray treatments two or three times a week. There was gradual but slow diminution in the number of leukocytes and in the size of the spleen. June 5, 1912, the red cells were 3,860,000; hemoglobin, 63 per cent.; leukocytes, 275,000, of which 24 per cent. were myelocytes. September 24 the leukocytes had fallen to 86,000 and the spleen was about half its original size. October 30, 1912, the leukocytes had increased to 143,000. Benzol treatment was begun at this date and on November 6 the total leukocyte count was 201,000. Then there was a gradual fall in the leukocytes, December 24, to 85,000, with a decrease in the number of myelocytes. December 30, the leukocytes had fallen to 40,000.

This patient was out of the hospital from November 22 to February 4, but was under constant observation. While out of the hospital he misunderstood the dosage of the benzol which he had been taking; that is 60 minims a day, and increased it to 160 minims. In about a week he suffered from burning in the stomach, eructations of acid fluid and gas and

finally an erythematous rash covered the whole trunk and body. This toxic erythema caused great discomfort and he was obliged to remain at home and to omit the benzol for about ten days.

When he resumed the benzol it was not as well borne as formerly and he was obliged to leave it off from time to time on account of the weight and heaviness after eating, eructations of acid fluids and gas and sometimes nausea. On January 14, his red cells were 5,030,000; hemoglobin, 82 per cent.; leukocytes, 54,000. This was just after he had taken 160 minims of benzol per day. On February 4, red cells, 4,100,000; hemoglobin, 70 per cent.; leukocytes, 97,800. The leukocytic formula difficult to make, but approximately as follows: polynuclears, 56 per cent., small lymphocytes, 3 per cent.; mononuclears, 11 per cent.; indentate nucleus, 4 per cent.; myelocytes, 18 per cent.; polynuclear eosinophiles, 1 per cent.; eosinophile myelocytes, 1 per cent.; basophiles, 6 per cent. On February 4 he reëntered the hospital. On February 11 the leukocytes were 86,600. From this time on patient showed a great deal of disturbance of stomach, including vomiting. This disturbance of stomach was finally so great that he was unable to take the benzol after February 15. On February 23, there was a slight rise of temperature and this increased day by day until the February 28, when it reached 103.8 with a rapid pulse and shallow respirations. At this date the red cells were 2,688,000; hemoglobin, 48 per cent.; leukocytes, 60,000. From this time on the patient presented all the evidence of a septic condition, one which is not uncommonly seen at the end in patients suffering from myelogenous leukemia under any form of treatment. On March 5, the red cells were 2,900,000; hemoglobin, 28 per cent; leukocytes, 151,000. Patient had subcutaneous hemorrhages with oozing of blood from the gums and a cough and expectoration of bloody sputa, consolidation of base of right lung. On March 8, red cells, 2,620,000; hemoglobin, 20 per cent.; leukocytes, 316,000. Patient passed into a somnolent state and died. Necropsy not obtainable.

It is possible that the poisonous dose of benzol disturbing the patient's stomach may have had some relation to the end result, but the end result was not benzol poisoning. It did not differ in any way from the septic state with hemorrhages under the skin from mucous membranes with septic temperature, rapidly increasing anemia which marks the end in this disease.

Case III.—J. L. B., farmer, aged fifty-two years, married, was admitted to the Presbyterian Hospital, June 18, 1912. Patient says that he has not been well for three or four years; has not been quite so strong as normal and has tired easily, with occasionally vertigo and headache. Since September, 1911, these symptoms have been worse with a gradual loss in weight. November 12, 1912, he had an attack of nausea with violent bloody vomiting and pain in abdomen. The next day he noticed black stools. The gums bled easily. Patient had slight cough, dyspnea on exertion and

edema of feet which disappeared at night. He noticed enlargement of abdomen and tenderness in upper left abdomen and at the sternum for a long time. He says he was never ill before.

Examination. Face, pale; general nutrition, poor; muscles, flabby; mucous membrane of mouth, pale; throat, normal; no enlargement of lymph nodes; lungs and heart, normal; spleen, enormously enlarged, lower border resting on crest of ilium and right border extending to median line. Liver just palpable at end of deep inspiration; not tender. Blood: Hemoglobin, 30 per cent. (Dare); reds, 2,360,000; whites, 640,000; differentiation: small lymphocytes, 12 per cent.; large lymphocytes, 24 per cent.; indentate nucleus, 2 per cent.; myelocytes, 33 per cent., of which 8 per cent. were eosinophiles; polynuclears, 29 per cent., of which 4 per cent. were basophiles. Urine: 1450 c.c. in twenty-four hours; specific gravity, 1.018; few hyaline casts and uric acid crystals.

Treatment and Result. Patient received *x*-ray treatments two or three times a week with regularity. July 14, hemoglobin was 46 per cent.; total leukocyte count, 370,000, and spleen slightly smaller. August 27, reds were 4,820,000; hemoglobin, 78 per cent.; whites, 118,000. September 11, 1912, total leukocytes were 28,000; October 6, 47,000. Then came a standstill in leukocytes; November 17, benzol treatment was begun with 7 minims three times a day, after a short period increased to 15 minims four times a day. The leukocytes gradually diminished in number, and December 17 the red cells were 4,600,000; hemoglobin, 72 per cent.; total leukocytes, 15,700, of which 11 per cent. were myelocytes. December 30, leukocytes were 13,500. Myelocytes still further diminished in percentage. January 9, 1913: reds, 4,000,000; hemoglobin, 76 per cent. (Dare); whites, 9800; differentiation: small lymphocytes, 10 per cent.; large, 6 per cent.; indentate nucleus, 2 per cent.; degenerated myelocytes, 6 per cent.; polynuclears, 76 per cent., 2 per cent. of which were of polynuclear and 1 per cent. of myelocytic type.

This patient left the hospital in January and returned to his home in Indiana, but has reported back to the hospital for blood examinations, etc., with regularity. On January 14, red cells, 5,100,000; hemoglobin, 74 per cent.; leukocytes, 7850. February 4, hemoglobin, 80 per cent.; leukocytes, 3500; the leukocytic formula: polynuclears, 63 per cent.; polynuclear eosinophiles, 5 per cent.; small lymphocytes, 18 per cent.; mononuclear cells, 5 per cent.; myelocytes, 4 per cent.; basophiles, 5 per cent.; February 25, reds, 4,900,000; hemoglobin, 78 per cent.; leukocytes, 4600. March 19, hemoglobin, 75 per cent.; leukocytes, 8600. April 16, red cells, 4,280,000; hemoglobin, 70 per cent.; leukocytes, 10,750; and benzol was begun in dose of 15 minims three times a day. April 25, red cells, 4,360,000; hemoglobin, 70 per cent.; leukocytes, 11,000. The leukocytic formula: polynuclears, 70 per cent.; polynuclear eosinophiles, 1 per cent.; small lymphocytes, 9 per cent.; large mononuclears, 8 per cent.; indentate nucleus,

5 per cent.; myelocytes, 6 per cent.; basophiles, 1 per cent. The patient's spleen was not palpable and it did not again become palpable until April 16. The floods in Indiana prevented the patient's visit to Chicago between March 19 and April 16. The patient has taken benzol with some discomfort, chiefly burning in stomach with eructations of gas and some heaviness after meals, but by taking a capsule containing benzol with three or four ounces of cream he makes but little complaint of disagreeable effects.

Case IV.—Mrs. F. A., aged twenty-eight years, secundipara, Russian, was admitted to Presbyterian Hospital, October 21, 1912. Illness began eight months before with weakness, lessened endurance, dizziness, dyspnea on exertion, and nervousness; these symptoms became progressively worse until the patient was obliged to give up work about ten weeks before admission. At that time a mass was noticed in upper left abdomen which caused a sense of dragging and weight; slight edema of ankles occurred at this time which disappeared at night. On admission patient complained of same symptoms with addition of fainting attacks, palpitation of heart, cramp in abdomen and constipation. Menstruation regular.

Examination. Patient very nervous, skin and mucous membranes pale; no lymph-node enlargements. Heart and lungs normal. Whole left abdomen filled by spleen, extending beyond the middle line on right. Liver palpable at end of inspiration; slightly tender. Pelvic organs normal. Urine normal. Blood: Hemoglobin, 50 per cent. (Dare); reds, 2,840,000; leukocytes, 680,000, of which 36 per cent. were myelocytes.

Treatment and Result. Patient was placed at rest on *x*-ray treatment three times a week. November 7, total leukocytes, 476,000. November 13, hemoglobin, 50 per cent.; total leukocytes, 546,000. At this time benzol treatment was begun in the dose of 15 minims four times a day, and November 19 the leukocytes had increased to 780,000; November 22, 600,000; December 2, 290,000; December 17, 46,000, at which time there were 9 per cent. of myelocytes. December 26, reds, 4,500,000; hemoglobin, 56 per cent. (Dare); leukocytes, 10,700; myelocytes had entirely disappeared. January 5, reds, 4,100,000; hemoglobin, 60 per cent.; leukocytes, 8500, with normal differentiation.

This patient has taken no benzol since January 9, and left the hopital on January 21. On January 21, reds, 4,140,000; hemoglobin, 58 per cent.; leukocytes, 4050; leukocytic formula: polynuclears, 69 per cent.; polynuclear eosinophiles, 5 per cent.; small lymphocytes, 20 per cent.; large mononuclears, 4 per cent.; myelocytes, 1 per cent.; basophiles, 1 per cent.

When the patient left the hospital she promised to report after ten days or two weeks for observation, but failed to come. Not responding to letters she was finally visited in her home on April 20. It was found that the spleen was just palpable, the patient had increased in weight but was pale. The red cells, were 1,800,000; the hemoglobin, 50 to 55 per cent.; leuko-

cytes, 2150; leukocytic formula: polynuclears, 58 per cent.; small lymphocytes, 33 per cent.; large mononuclears, 5 per cent.; indentate nucleus, 2 per cent.; myelocytes, 1 per cent.; eosinophile myelocytes, 1 per cent. In the three months which had elapsed since the last observation the red cells have fallen from 4,140,000 to 1,800,000 and the leukopenia was more marked. The hemoglobin remained nearly the same. The patient expressed herself as feeling well, disinclined to come back to the hospital and husband was also averse to her returning for further treatment. The blood picture at this time is much like that of a pernicious anemia, the red cells, however are not deformed nor are there many very large or small cells. The notable thing is the high color index, the leukopenia and the relative increase of the small lymphocytes. The present condition is suggestive of the possible production of a hypoplastic marrow coincidently with the use of benzol in the treatment. On May 1, the patient was again visited in her own home and found to be improved as compared with the condition of April 20. Red cells, 2,180,000; hemoglobin, 50 per cent.; leukocytes, 3950; leukocytic formula: small lymphocytes, 21 per cent.; large mononuclears 4 per cent., indentate nucleus, 6 per cent.; polymorphonuclears, 66 per cent., and in making the differentiation three normoblasts were found.

Case V.—Mrs B. H., aged forty-one years, secundipara, German, was admitted to Presbyterian Hospital, December 5, 1912. In June, 1912, the patient began to have pain in the abdomen in the form of cramps, and heaviness in upper left abdomen; soon after this a mass was discovered in that region. This caused a sense of dragging and soreness which was aggravated by walking. The appetite was poor. Weakness gradually increased; weight declined from 135 to 117 pounds. On admission the patient complained of heaviness, fulness, pressure and tenderness in left upper abdomen, and that there was a tumor there. She was weak, had dyspnea on exertion, palpitation of heart, no appetite, constipation, amenorrhea of six weeks' duration, and a rather profuse leucorrhea. Thirteen years ago at birth of last child, patient suffered from laceration of the perineum and neck of uterus which was repaired, but had suffered from leucorrhea since that time. Otherwise patient had been healthy.

Examination. Mucous membranes pale; skin rather dark from a diffuse pigmentation. Slight enlargement of lymph nodes in the posterior triangles of neck, axillary region, supratrochlear and in groins. Heart and lungs normal. Spleen, right border almost to middle line, lower border to iliac crest. Liver moderately enlarged and slightly tender. Pelvis: uterus retrodisplaced and movable; appendages seem normal; slight laceration of cervix uteri. Urine: Specimen normal and later examinations of twenty-four hour collections normal. Blood: reds, 4,500,000; hemoglobin, 66 per cent.; total leukocytes, 45,000, of which 61 per cent. were small lymphocytes, 6 per cent. large lymphocytes, 34 per cent. polynuclears, no myelocytes and no eosinophiles.

Treatment and Result. Benzol and Röntgen treatment were begun at once, and December 9 the total leukocytes were 19,000. December 18, reds were 4,420,000, hemoglobin 58 per cent., total leukocytes 5800, giving practically the same differentiation. December 26, leukocytes 6000, small mononuclears 35 per cent., large 21 per cent., polynuclears 41 per cent., with 6 per cent. of eosinophiles; indentate nucleus 1 per cent. January 5 the leukocytes were 5900, hemoglobin 68 per cent., reds 4,120,000.

This patient left the hospital in the latter part of January and returned in March for a gynecological operation of a plastic kind. On April 3, her red count was 2,500,000; hemoglobin, 65 per cent.; leukocytes, 2,450,000, of which 14 per cent. were small lymphocytes, 8 per cent. large mononuclears, 70 per cent. polynuclears, 4 per cent. polynuclear eosinophiles. On April 15, red cells, 3,130,000; hemoglobin, 60 per cent.; leukocytes, 3600. This patient had no benzol after January 11. Splenic enlargement and lymph nodes had all disappeared at that time. The leukocytes continued to fall in number and at the same time there was a rather notable decrease of red cells following the gynecological operation. May 1, red cells, 3,340,000; hemoglobin, 65 per cent. (Dare); leukocytes, 6,000; leukocytic formula: small lymphocytes, 21 per cent.; large mononuclears, 2 per cent.; indentate nucleus, 2 per cent.; polymorphonuclears, 75 per cent.

Patient is now in her own home and the only complaint is of some pain in the pelvic region which has been present since the gynecological operation in March. The general health is very much improved.

General Remarks. We have continued to give the benzol, as a rule, in gelatin capsules filled at the time of administration. Most patients desire to take the drug in this form rather than in the emulsion. Those patients who did not object took from 5 to 15 c.c. of olive oil with the capsules. Others used from 30 to 100 c.c. of a good cream in place of the oil. The capsules were best borne when taken soon after the meal. Only one or two patients have expressed a preference for the emulsion. This has been made up by the hospital druggist with 15 minims as the average dose in two to four teaspoonfuls of the medium. A good many of the patients complained of eructation of gas, tasting and smelling of the benzol. A burning in the stomach was complained of by a few; some of the patients complained of dizziness while taking the drug, but they also continued to complain of the same symptom in the interval between the periods of its use. The maximum dosage

has been 4 grams per day. It has not been found necessary to give a larger amount to produce the desired effect.

In Case II who had inadvertently taken 160 minims a day for a week while away from the hospital and who suffered from a toxic erythema, the drug was not well borne thereafter, but as he soon showed signs of the not unusual septic state which often occurs in the last stages of the disease and inasmuch as such patients usually suffer from nausea, vomiting, etc., it is not improbable that it was this condition which prevented the use of the drug at that stage of his illness.

We have not used the drug hypodermically and from the ill effects reported from its used by Dr. Klein whose record of patients has been quoted *in extenso* in this paper, would it seem wise to do so?

As one reads of the very large dosage of benzol which he exhibited in some of his records and of the serious result which followed in three of the patients, one cannot help but be impressed with the fact that benzol is a toxic agent when used in large doses. Or, perhaps it would be better to say that in certain individuals it may produce unhappy results if given in large dose.

The chief notable results of benzol medication which were noted in my former report have been confirmed by further observation. These will bear repetition.

1. There is a tendency to a rise in the leukocytic count of the peripheral circulation in the first few days of medication.

2. There is a rapid fall in the number of leukocytes in the peripheral circulation in most patients under full safe medication within ten days or two weeks after the beginning of the use of the drug.

3. There is a correspondingly rapid diminution in the size of the spleen and also of the liver and this is much more rapid than the diminution which occurs in those organs under Röntgenotherapy alone.

4. As a rule there is an improvement in the red cell count and in the hemoglobin of the peripheral circulation.

5. In lymphoid leukemia the drug apparently acts more rapidly than in the myelogenous type with a very rapid fall in the number of the white cells in the blood, but there is not the same improvement in the red cell count and hemoglobin as in the myelogenous type.

6. Stained specimens of the blood show a very early degeneration of the leukocytes; the mononuclear types become granular and usually these granules are basophilic. The polynuclear cells show not only granules of degeneration, but some of them are shrunken to the size of the normal red cell. The blood picture is such that one cannot make a leukocytic formula which will correspond with anything known. In consequence the differential count made of the reported patients varies from period to period because the differentiation has been made by different individuals and the individual equation accounts for the difference.

7. Most patients improve in a general way and especially those who are intelligent enough to have a conception of the serious nature of the illness.

8. In all of the patients reported in my series, the *x*-ray had been used at some time. Consequently I am still unable to give an experience of the use of benzol alone in the treatment of leukemia.

However, in the reports from others mentioned in this paper, patients have been treated with benzol without *x*-ray with good results.

9. I am still more than ever impressed with the powerful effects of benzol. Apparently it has a distinct effect upon the medulla of the bone, and paradoxical as it may seem, it apparently renders the leukoblastic marrow less active and in the myelogenous type seems to make the erythrocytic marrow hyperplastic.

As pointed out in a former paper, if poisoning by benzol may produce a hypoplastic bone-marrow and an aplastic anemia one must bear in mind the dangerous nature of the remedy and test it out cautiously upon individual patients.

10. I am perfectly satisfied with the experience I have had, that benzol is a valuable agent in the treatment of leukemia, and it will be especially valuable in the treatment of those patients who may not be able to command Röntgenotherapy. Experience seems to show that benzol is more efficacious in combination with the *x*-ray treatment.

DISCUSSION

Dr. R. C. Cabot: I can reinforce what Dr. Billings has said; benzol is indeed a two-edged sword. One case in which I used it died very promptly; the benzol was not to blame, however; he would have died anyway.

In the chronic cases we know that remissions may occur quite independently of treatment. But in view of the striking results obtained by Dr. Billings in a disease for which we have no other remedial agent, we can welcome even a two-edged sword.

Dr. Jos. S. Miller: I have had two cases of leukemia in which I used benzol concurrently with *x*-ray. One of the cases, a man, was much improved. The other, a woman, showed no improvement under benzol alone; then, with *x*-ray therapy added, there was very marked general improvement.

In a recent work, Pappenheim has insisted that benzol does not in fact destroy leukocytes; that their disappearance is due to other causes.

Dr. James B. Herrick: I have had the privilege of seeing some of these patients treated by Dr. Billings; those who have done so surely must be impressed with the value of benzol in the treatment of leukemia. I have used the remedy in three cases in which some gastric disturbances were produced.

In one case in which striking benefit occurred, no improvement followed the use of benzol alone, but could be noted at once when very small doses of *x*-ray were added. This patient was sent home in good condition and with statisfactory blood findings, but two weeks later she suddenly died with symptoms of multiple cerebral hemorrhage. This accident, perhaps, cannot be chargeable to the benzol.

Dr. James Tyson: Was the urine concurrently examined for albuminuria during the use of benzol in these cases?

It would seem that the drug is a powerful irritant and apt to do renal damage.

Dr. A. McPhedran: It is important to inquire as to the character of the leukocytes rather than their number. I recall a case of myelogenous leukemia in which under arsenic the leukocytes fell from a high count to 4000; but they were abnormal leukocytes.

Dr. Billings: Dr. Miller quoted Pappenheim to the effect that benzol does not destroy leukocytes; I think anyone who has studied the blood in

these cases could have no doubt that the white cells are actually disintegrated.

As to the uric acid output, there is no increase.

As to the effect of benzol therapy on the whole blood-making apparatus, it may be said that in all patients showing improvement there is not only an actual fall in the white cells, but the red count and the hemoglobin index rise.

In myelogenous leukemia there is for the first ten days of treatment a great increase in the white count, but there is a steady decrease thereafter. This is not so in splenic leukemia.

CULTURAL RESULTS IN HODGKIN'S DISEASE[1]

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The publication at this time of the result of our endeavors to cultivate an organism from the tissues of Hodgkin's disease cases is occasioned by the publication by Negri and Mieremet[2] of the successful cultivation from two cases of Hodgkin's disease of a diphtheroid organism which they designate as the Corynebacterium granulomatis maligni.

While Hodgkin's disease, or malignant granuloma of the lymphatic apparatus, has of late years come to be generally regarded as of infectious nature, the etiological agent has remained undetermined. The work in this country of Reed[3] and of Longcope[4] showed definitely that the condition was independent of tuberculosis, and that the theory supported by Sternberg[5] that it was a manifestation of the activity of the tubercle bacillus could not be maintained.

In 1910 Fraenkel and Much[6] reported that by treating Hodgkin's glands with antiformin they had found in the sediment, in twelve out of thirteen cases, certain granular, Gram-staining, but non-acid-fast bacilli, which they considered to be non-acid-fast tubercle bacilli, "possibly identical with the ordinary tubercle bacillus," but

[1] This work has been aided by a grant from the Rockefeller Institute for Medical Research.

[2] Centralbl. für Bakteriologie, 1913, lxviii, 292.

[3] Johns Hopkins Hosp. Reports, x, 133.

[4] Bull. of the Ayer Clin. Lab., 1903, No. 1.

[5] Zeit. f. Heilkunde, 1898, xix, 21.

[6] Zeit. für Hygiene, 1910, lxvii, 159.

"more probably a special form of the tubercle virus" or at least "belonging to a related group of organisms."

In the present year, Negri and Mieremet[1] have reported the successful cultivation upon Bordet's medium (blood-glycerin-potato-agar), from two cases of Hodgkin's disease, of an organism which falls within the diphtheria group, and further agrees in morphology with the forms described by Fraenkel and Much. The organism is a non-acid-fast, Gram-staining bacillus, growing luxuriantly at body temperature, and is a facultative anaërobe. Perhaps its most striking feature is its pleomorphism. The organism showed such variability in form that it was only after isolation of a single organism and cultivation of it that the authors were satisfied that they were dealing with a pure culture. In various media the following forms were found: plump, short rods, some so short as to resemble coccobacilli, these latter forms predominating or being exclusively found in old cultures; small, thin bacilli with polar staining; comma-shaped bacilli; granular rods of variable size, often of considerable length; branching forms; and on all media, club-shaped involution forms and large spherical forms. This organism is resistant to antiformin, and the authors consider it identical with the organism described by Fraenkel and Much.

In a study of Hodgkin's disease extending over the past five years we have made various attempts to secure cultures from material removed at autopsy and at operation. The first attempts were made with ordinary media and were unsuccessful. In Case IX of our reported series,[2] cultures were made at operation in October, 1910, by planting portions of glands in bouillon, but apparently in this case there was a complicating infection, as only a streptococcus growth was obtained. In Case V of the series, attempts were made in January, 1912, to secure cultures from the enlarged mesenteric glands at autopsy, but postmortem invading organisms completely overgrew the media.

After these failures it was felt that special media must be used, and as at this time we felt from certain observations that the organism was probably one of the higher forms of bacteria if not a fungus, media appropriate to the growth of these organisms were selected.

[1] Loc. cit.

[2] Johns Hopkins Hosp. Bull., 1911, xxii, 368.

Dorset's egg-medium and glycerin-phosphate-agar were first tried. The first opportunity for their use came in an operation by one of us (J. L. Yates) for the removal of a large group of cervical glands on February 13, 1912, from a woman patient.

The essential points in her history are as follows:

Female, white, aged thirty-three years. When first seen in October, 1911, the patient showed in the right side of her neck a group of enlarged, discrete glands extending from the mid-clavicular region upward in the posterior triangle practically to the attachment of the sternocleidomastoid. This group of glands had shown progressive enlargement during the year previous. Except for one small gland below the clavicle on the right side and a rather large gland in the right axilla, no further enlargement of lymphatic glands was noted at this time. The spleen was not palpable. The tonsils were enlarged. On October 10 a von Pirquet test and a Wassermann reaction were both negative. On October 23 the large axillary gland was removed for diagnosis. In section it showed hyperplasia of lymphoid and of endothelial elements, with giant cells of the endothelial type and of the megalokaryocyte type, disappearance of the architecture of the gland, and a beginning diffuse sclerosis and marked eosinophilic infiltration. December 11 tonsillectomy was done, and on February 13, 1912, the large group of glands in the right side of the neck with the intervening sclerotic tissue were removed *en masse*.

After removal, the group of glands was incised, and, with the observation of the strictest aseptic technique, portions of the glands and of the interglandular tissue were planted upon the surface of slants of the egg-medium and of the glycerin-phosphate-agar. The tubes were sealed with paraffin and incubated at 37°. The tubes were apparently sterile at the end of ten days' incubation, but they were left undisturbed in the incubator, and at the end of three weeks' time a slight growth was noted on one tube. On March 12, two of the egg-tubes and one tube of glycerin-phosphate-agar showed pure cultures of a diphtheroid organism, with many clubbed-shaped involution forms, with granular and barred rods and evidently branching filaments. The organism was Gram-staining.

Subcultures were made from the original tubes upon blood-serum, egg, glycerin, agar, and the ordinary media. The organism proved to be a rather feeble grower under the conditions under which its growth was attempted at that time. On blood-serum in twenty-four hours there were obtained the characteristic shining opaque white colonies. On agar the growth was slow, the streak at first being of a grayish, glistening, translucent appearance becoming more opaque with age. In bouillon there was a scanty growth, which gradually settled to the bottom as a somewhat slimy precipitate. No turbidity of the medium occurred. Milk was not coagulated. Its reaction was changed but little if any.

The growth was tested on guinea-pigs, and while the results were unsatisfactory in a sense, it was determined that the animals would survive inoculation with a heavy dosage of a twenty-four-hour culture for ten days at least. Through an accident this culture was lost before thorough testing of it could be done.

Further opportunities for obtaining cultures were not obtained until January, 1913, when, through the kindness of Dr. W. J. Mayo and the coöperation of his staff, the courtesies of the clinic at Rochester were extended to us.

On January 9, 1913, cultures were made from a cervical gland removed for diagnostic purposes from a patient with the following history:

Female, white, aged thirty-four years. Four years previously she noticed a swelling on the right side of her neck, followed by the appearance of other small tumors. Ten months before date enlarged glands appeared on the left side of the neck and in the right axilla. Six weeks previously glands appeared in the left axilla. Physical examination revealed, in addition to these nodules, a mediastinal mass, a six months' pregnancy, over which were felt discrete, firm nodules which slipped under the examining hand. Nose and throat examination revealed a hypertrophic rhinitis, causing some nasal obstruction, and also enlarged tonsils. Red-blood cells, 4,480,000; leukocytes, 12,400.

Pathology of gland. The test gland shows microscopically loss of architecture, with lymphoid and endothelial hyperplasia, the presence of many endothelial giant cells, a beginning fine

sclerosis and eosinophilic infiltration. There is slight invasion of the capsule.

Pieces of the gland were planted on egg-medium and on Loeffler's blood-serum. The tubes were sealed and incubated. On January 17 one egg-tube showed the characteristic clubbed and granular diphtheroid forms seen in the first culture; but associated with a growth of B. subtilis. One serum-tube showed a pure culture of the diphtheroid organism; and one serum-tube showed the presence of a white staphyloccus. Three other tubes were sterile.

Subcultures of the diphtheroid organism were made from the serum-tube on to other media; particularly egg-medium, glycerin-phosphate-agar, and plain agar. The growth proved to be luxuriant on those. The top of the streaks had a grayish, glistening appearance, while the lower part of the streaks were at first of an opaque white appearance, gradually assuming a slight yellowish color deepening in very old cultures, as glycerin agar, to a brownish. Smears from the older cultures showed such a pleomorphism, and there were so many coccoid forms it was at first thought we were dealing with a mixed culture of bacillus and coccus. It was only after growth of many generations upon egg-medium, on which the culture is of a pure bacillary type during the first twenty-four hours, and after shaking the culture with sand and plating from a further dilution, which gave colonies of a uniform and characteristic type, that we became assured we were dealing not with a symbiosis of coccus and bacillus, but with a pleomorphic organism.

A third successful cultivation was made February 15, 1913, from a cervical gland from the following case from the Mayo clinic.

Married female, white, aged thirty-eight years, with marked enlargement of the cervical glands and rather general glandular enlargement. The illness began with involvement of the cervical glands two years previous to date.

The gland removed for diagnosis showed extreme sclerosis, but with scattered alveoli-like areas in which the characteristic elements of the Hodgkin's lymph gland, the endothelial cells, giant cells, and lymphocytes were preserved. Eosinophilic infiltration was well marked.

After one week's cultivation there were secured from two tubes one of Loeffler's serum and the other of egg-medium, a pure culture of a diphtheroid, pleomorphic organism apparently identical with that secured from the previous case, and showing the same cultural characteristics. It was put through the same procedure to determine the purity of the culture and gave the same result; that is, after shaking with sand and diluting and plating, all the colonies on the plates were of a uniform character.

In the interval between the last two cases, attempts were made to secure cultures from two other cases but they resulted less successfully. The first of these attempts was at a postmortem, January 15, 1913, on the following case:

Female, white, aged fifty years (patient of Dr. Reeves, of Albany, Wis.). The glandular swelling had first appeared in the left cervical region two years before. The cervical group of glands had been removed about six months previous to the patient's death At the postmortem examination there was found rather general glandular involvement, but especial enlargement of the mesenteric and retroperitoneal glands and of the lymphoid elements of the spleen. There was also a chylous ascites, well-marked anemia, and emaciation. Old pleural scars were noted at the pulmonary apices and one calcified focus in a bronchial lymph gland. No other signs of tuberculosis were seen.

Microscopically, the abdominal glands showed a well-marked hyperplastic Hodgkin's disease picture, with beginning diffuse sclerosis, while the splenic lesions showed a more advanced sclerotic condition.

On one Loeffler serum-tube, in which was planted a piece removed from the interior of the spleen, there was noted a growth on the tissue itself of typical polar-staining diphtheroid organisms, but, for some reason unascertained, they would not "catch on" to the medium, and attempted subcultures from scrapings of the tissue on both the egg-medium and serum proved negative.

The second case was the following from the Mayo clinic on January 31, 1913:

Male, white, aged thirty-three years. The patient had had an an abscess of a tooth six months previously. About three weeks

before coming to the hospital patient had noticed a painless swollen gland in the left supraclavicular region. This had increased in size during the time of observation. The large gland removed was of a uniform medullary appearance on gross section, and microscopically showed lymphoid and endothelial hyperplasia, with the presence of giant cells, beginning diffuse sclerosis and eosinophilic infiltration. The architecture of the gland was destroyed.

Unfortunately for the success of cultural investigation, this gland had been handled and incised before the plants upon the media were made. Four days after incubation of the tubes was begun, there was found upon one of the serum-tubes a growth of the typical diphtheroid organism, but in association with a coarse bacillus of the B. subtilis type. As at this time our efforts were being directed to the elimination of the supposed coccoid contamination of our second culture, no attempt was made to separate the diphtheroid organism from this last mixed culture.

While the authors have made no systematic attempt to find the organism described in histological preparations from the glands of Hodgkin's disease patients, one case should be recorded as of interest in connection with the cultural results. Portions of the organs from a girl, six years of age, a patient of Dr. Ogden, of Milwaukee, who died in a severe vomiting attack, were received in the laboratory. The Peyer's patches of the intestine and the mesenteric lymph glands showed the changes of early Hodgkin's disease, which from clinical and postmortem evidence must have been primarily intestinal in origin. Upon staining the sections by the Gram-Weigert method, the only organisms found, save for the surface intestinal bacteria, were groups of polar and granular-staining diphtheroid organisms lying deep within the enlarged Peyer's patches.

To summarize our cultural results: In three cases of Hodgkin's disease we have secured a pure culture of a pleomorphic diphtheroid organism. In two other cultural attempts the organism has been recognized but has not been secured in pure culture, and in a sixth case a similar organism, morphologically, has been stained in the lesions of a primary intestinal Hodgkin's case.

The detailed biological reactions of this diphtheroid organism

have as yet not been completely worked out by us. The strain recovered from the second case, however, has been found to grow readily at 37° on the media used to secure the cultures and an ordinary agar-agar. On glycerin-phosphate-agar the growth is almost as luxuriant under strict anaërobic as under aërobic conditions. For luxuriant growth, marked moisture of the medium seems necessary. On a relatively dry medium growth is slow, and the organisms are found to develop as the long forms, granular banded, and with many club-shaped involution forms. Branching forms are also noted. These forms are especially well-developed on the egg-medium, where they also seem to have a tendency to cohere, so that in stained smears one gets many small groups of organisms radially arranged, with clubbed peripheral elements, somewhat suggestive of a minute actinomyces colony, as seen in section. On moist serum-tubes with luxuriant growth the organisms are short and plump, with polar staining. Many of these forms are coccoid. We have noted also, as emphasized by Negri and Mieremet, that in all old cultures coccoid forms predominate, and also that large spherical involution forms are present. A colony or a streak which at twenty-four hours shows entirely the bacillary form, will twenty-four or forty-eight hours later show an apparent outnumbering of the bacilli by the coccoid elements.

The organism stains by the Gram methods, though the short plump forms hold the dye less strongly than the longer bacillary forms. It is not acid-fast. No spore formation has been noted.

The growth of the organism is at first glistening and grayish, but becomes more opaque and of a white color. Apparently depending somewhat upon the reaction of the media, there may be in some early cultures a slight greenish-yellow tint produced. Old cultures upon glycerin-phosphate-agar become brownish, and the media itself darkens.

Gelatin is not liquefied. There is no early change in reaction in litmus milk. Bouillon is not clouded by the growth. Flecks appear along the side of the tube, and a slimy deposit gradually accumulates at the bottom.

Plate cultures show a rounded colony with quite regular edge, a fine stippling of the growth and a central dark spot. The colonies

are of a glistening gray color at the end of twenty-four hours, becoming gradually of an opaque white color.

Altogether our studies thus far seem to indicate that we are dealing with the same organism described by Negri and Mieremet, and while our results taken with theirs cannot be said to indicate positively that we are dealing with the cause of Hodgkin's disease, yet they are strongly suggestive. The morphological elements obtained by Fraenkel and Much by the antiformin method in twelve out of thirteen cases are so similar to the organism cultivated by us that we find added support as to the importance of the organism in the disease in their findings. Ultimate proof can come only from an extended series of cultures, or from animal experimentation. The latter test is now in progress in this laboratory with a variety of animal species. Should the relation of the organism to the disease be established we would suggest Corynebacterium Hodgkini as a more appropriate name for the species than the trinomial designation suggested by Negri and Mieremet.

Although the utmost efforts were made to prevent carrying in organisms from the skin, when removing glands for cultural investigation, in almost every case studied one or more tubes have shown the presence of a white staphylococcus. This, when taken in connection with the polymorphonuclear leukocytosis, which occurs late in the disease, has suggested that possibly a secondary infection plays a part in the development of the disease. This feature also needs further investigation.

HEREDITY WITH REFERENCE TO CARCINOMA AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN DURING 1895–1913

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The statistical study of carcinoma is regarded by many writers as having been carried as far as it can profitably go; and certainly but little that is new has been gained by this method during the last decade. Nevertheless its possibilities have not been exhausted; and it is highly desirable that the whole neoplasm problem in all of its aspects be attacked again from the statistical standpoint but in a somewhat different way. Practically all of the old statistical studies of neoplasm, particularly those of carcinoma, were based upon mortality reports; or if not upon these, upon morbidity reports based upon clinical diagnoses. In very few instances only has the statistical study been carried out upon the basis of the records of a diagnostic pathological laboratory. Statistics of neoplasm from such a source must be of infinitely greater value than those founded upon mortality statistics. In the records of the diagnostic laboratory the diagnosis is based upon the histological examination, and the percentage of error is reduced to a minimum. In the mortality statistics, on the other hand, the diagnoses are chiefly clinical, and subject to the wide error inherent in the clinical diagnosis of "tumor," "neoplasm," "cancer," and the like. Moreover, the material coming to the diagnostic laboratory is seen at an earlier age—usually two to five years—than the mortality age. In studies relating to the age-incidence of any form of neoplasm it is evident that the records of the pathological laboratory will be

much more trustworthy than the mortality statistics for that neoplasm. It is also possible many times in the diagnostic laboratory to follow the course of a neoplasm over a definite period, so that important practical knowledge may be gained as to rate of growth, recurrence, healing, metastases, etc.

The following study of the influence of heredity on carcinoma is taken from the records of the pathological laboratory of the University of Michigan during the years of my service from 1895 to 1913. During this period 3600 cases of neoplasm of all varieties have been studied, either in material taken for practical diagnosis or obtained by autopsy. Of these 3600 cases some 1600 were cases of carcinoma as shown by the microscopic diagnosis. Practically every variety of carcinoma described in the literature, and a few others as well, are to be found in this material; and the same is true of the other forms of neoplasm. While carcinomas of the breast, uterus, and lip form the greater part of the cases examined, all other localizations are represented. The material has also another great advantage; about 90 per cent. of it is derived from the general population of the State of Michigan. The University Hospital being a State hospital and not a charity institution gives then a much more representative population than would be found in the charity hospitals of the greater cities.

The difficulty of obtaining a family history in the case of patients in charity hospitals is well known. Few of them know the cause of death of their grandparents or of other members of that generation. The same thing is true though to a less extent of the patients from whom the material serving for this study was obtained. Therefore what worth this study may have must be a positive one; the negative findings cannot be taken as absolute. In about 600 of the cases of carcinoma no family history at all was obtainable; in the majority of those in which a family history was obtainable the details are very meager. In spite of all these handicaps a surprisingly large number of cases give a family history of carcinoma—about 15 per cent. of all cases in which a statement covering the family history is obtainable.

The existence of a family susceptibility to carcinoma, denied by many writers, affirmed by others, has again become a question

exciting lively interest as a result of the studies of endemic carcinoma in mice. These investigations appear to show that certain family strains of mice do not develop spontaneous tumors, and that, further, such strains are resistant to tumor transplantation from other mice. Other family strains show a high frequency of spontaneous tumors, and in such strains transplantation may be successfully carried out. It would appear then that such strains possess a familial predisposition or susceptibility to the development of neoplasm, and that intrinsic or inherited factors play some part in the development of neoplasms. Bashford denies this, and Tyzzer, who carried out breeding experiments with animals representing such different strains, was unable to find that the transmission of the predisposition to neoplasm followed the laws of heredity.

On the other hand, a family predisposition in the human species to certain forms of neoplasm has long been recognized, particularly in the case of certain benign neoplasms (fibroma, lipoma, chondroma osteoma, angioma, leiomyofibroma, glioma, neurofibroma, papilloma, adenoma, and cystadenoma), and less marked in the case of certain forms of sarcoma and carcinoma. While the existence of such a predisposition is generally accepted by the text-books on pathology, no good statistical studies exist of the hereditary occurrence of these neoplasms.

Cancer surveys of living patients, as conducted in Germany some years ago, have given little information concerning the family occurrence of neoplasms, chiefly for the reason that it is practically impossible to trace the members of a given family through more than one or two generations, and unless all of the members of the family for several generations can be considered no accurate conclusions can be drawn. The difficulties attendant upon such a statistical study are very great, and except in rare cases complete family records of cancer incidence are not found in the literature. One of the most striking is Broca's case,[1] also quoted by Levin, who criticises the method of investigation because no comparison was made between the number of the affected and unaffected

[1] Wolf, Die Lehre von den Krebskrankheiten, Jena, 1907.

members in each generation. If the total number of ascendants is not considered, and only those affected by carcinoma picked out, a family may appear to be a cancer family when in reality the proportion of cancerous to non-cancerous members is very small. As Levin states, Broca's family might give very different results if studied from the standpoint of all its members.

Levin, to my knowledge, is the only one who has attempted the statistical study of cancer and heredity from the standpoint of the entire family. He collected data from five families,[1] two families fairly complete and three fragmentary. In the families studied he noted that they were characterized on the whole by the occurrence of cancer of the intestines in the males, and cancer of the breast in the females. His charts show that the incidence of cancer in these families is not greater numerically than would be found in the population as a whole, but that the occurrence of "cancerous fraternities" (a fraternity in which one or more members suffer from cancer, with a history of cancer either on the maternal or paternal side, or both) speaks for some influence of heredity on cancer, in other words, a cancerous fraternity must mean the union of two germ-plasms each of which is characterized by the presence of germ cells that are non-resistant to cancer.

In my material of 3600 cases of neoplasm examined pathologically there were 1600 cases of carcinoma. About 1000 of these gave fairly good family histories with ages. A smaller percentage (30) gave detailed histories. From these are taken the families showing multiple occurrence of carcinoma. In many of these all members of the family for three generations are given, in others the records are incomplete. Four families give complete records of the descendants of the cancerous grandparent. The incidence of cancer in these families is so striking that it can be interpreted as showing an inherited susceptibility to cancer.

CANCER FAMILIES

Family G. In this family a fairly complete survey of the two generations derived from a cancerous grandfather with a tradition-

[1] Zeitsch. f. Krebsforschung, 1912.

ary history of cancer in his line and a grandmother with a normal family history was made. From these there were ten children, five males and five females. Two of the daughters died of cancer of the uterus at fifty-five and forty years, while two sons died at forty-two years of cancer of the stomach, and a third one at forty-five years of cancer of the abdomen. All five of these individuals were married to normal partners without a family history of cancer, and all had issue, as follows: Oldest daughter who died at fifty-five years of cancer of the uterus, had ten children, one daughter operated at forty-two years for cancer of the uterus and still living;

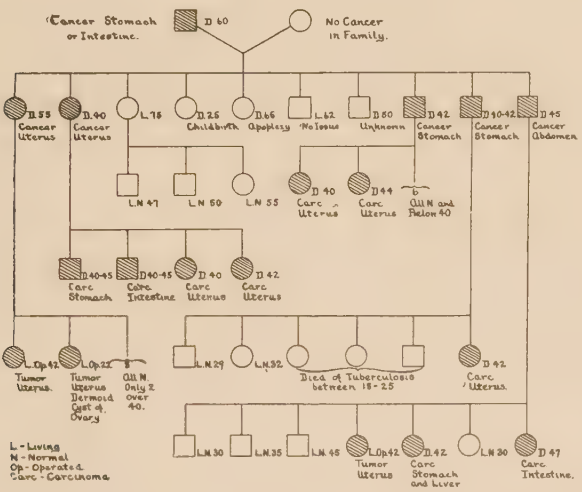

FIG. 1

another daughter operated at twenty-two years for uterine tumor and bilateral dermoids of ovary, and still living (Fig. 1). The remaining eight children are all living and well, only two being over forty years of age. The second daughter, who died at forty years, of cancer of the uterus, had four children, two sons and two daughters, all dying of cancer at about the age of forty, the two sons dying of cancer of stomach and intestine, and the two daughters of carcinoma of the uterus. The third daughter, living and well at the age of seventy-five years, had three normal children living at ages of forty-seven, fifty, and fifty-five years. Four children had

no living issue. The eighth child, a son, died at forty-two years, of cancer of the stomach. His wife was of normal family history. They had eight children of whom two daughters have died of cancer of the uterus at forty and forty-four years, while the remaining six are all living and well below the age of forty years. The ninth child, a son, died of cancer of the stomach at forty or forty-two years of age. He left six children from a marriage with a woman of non-cancerous family history. One daughter died at forty-two years, of cancer of the uterus, three children died of tuberculosis between eighteen or twenty-five years, while two others are living and well at ages of thirty-two and twenty-nine years. The tenth son died at forty-five years, of cancer of the abdomen, most probably primary in the stomach. He left, from a marriage with a woman of non-cancerous family, seven children, of whom one died at forty-two years, of cancer of the stomach and liver, another at forty-seven years, of cancer of the intestine, while a third was operated at forty-two years for tumor (cancer) of uterus, and still lives in apparent good health. Four others are living and normal at ages of forty-five, thirty-five, thirty, and thirty years.

Of the forty-eight descendants of the cancerous grandfather, seventeen have died or been operated upon for "cancer." The preponderance of carcinoma of the uterus (10 cases) and of the stomach (7 cases) is very striking in the family history.

Family F. In this family the maternal grandmother died of tumor. Her non-cancerous brother had two children who both died of "cancer." Her only son died at sixty-one years of dropsy. He married a woman who had two brothers who died of cancer of the stomach (Fig. 2). She herself died of Bright's disease at seventy-five years. Her mother died of heart disease. The three daughters of this pair who show a double family history of susceptibility to cancer all had neoplasms, the oldest was operated for tumor ("cancer") of uterus and is living, the second child was operated at fifty-one years for myosarcoma of uterus, while the third daughter died of cystic tumor of the ovary. In this family history the preponderance of stomach and uterine neoplasms is also shown.

Family P. The paternal grandfather had a nephew who died of cancer of the lip. In the first filial generation there was one

daughter who died at thirty-five years of cancer of stomach and liver, a son who died at sixty years of cancer of the lip, and another son who died at eighty-six years of cancer of the scalp and cervical lymph nodes (Fig. 3). This son married a non-cancerous woman whose only sister had died at forty-seven years of cancer of the rectum. From this union came thirteen children, ten of whom (five

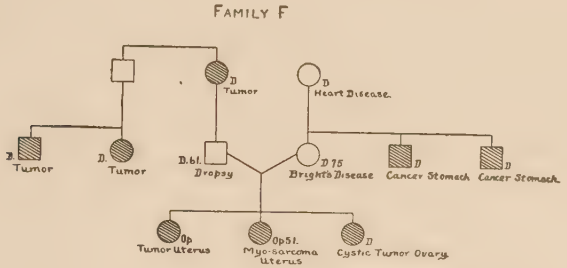

FIG. 2

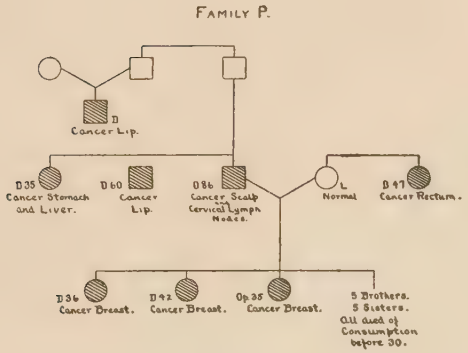
FAMILY P.
D Cancer Lip.
D 35 Cancer Stomach and Liver.
D 60 Cancer Lip.
D 86 Cancer Scalp Cervical Lymph Nodes.
L Normal
D 47 Cancer Rectum.
D 36 Cancer Breast.
D 42 Cancer Breast.
Op 35 Cancer Breast.
5 Brothers. 5 Sisters. All died of Consumption before 30.

FIG. 3

brothers and five sisters) all died of pulmonary tuberculosis before the age of thirty years, while three remaining daughters had carcinoma of breast, two dying at ages of thirty-six and forty-two years, and one operated at thirty-five years.

FAMILY S. The paternal great-grandfather died at about seventy years of cancer of the stomach. His only son died at about sixty years of cancer of the stomach, having married a woman who died

at about fifty years of cancer of the breast (Fig. 4). They had six children, all of whom died of cancer, two daughters died at eighty and sixty years of cancer of the breast, and another at sixty years of multiple carcinoma of breast, bladder, and rectum. Two sons died of cancer of stomach at ages of seventy-five and forty years, the third son dying of cancer of some internal organ, most

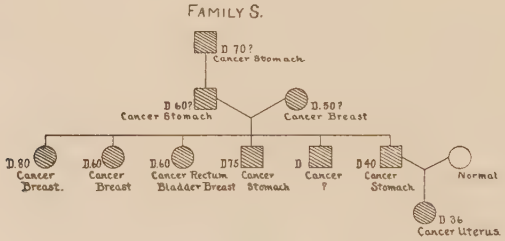

FIG. 4

probably the stomach. Only one son had issue, by marriage with normal line. The only child died at thirty-six years of cancer of the uterus. Of the eight descendants of the cancerous great-grandfather all died of cancer. As in Family P., the occurrence of carcinoma in both paternal and maternal lines apparently strengthens the susceptibility, both families becoming extinct.

CANCEROUS FRATERNITIES

These are of much more frequent occurrence in the case-histories of carcinoma than the striking family histories given above (Fig. 5). The reasons for this are obvious: few individuals of the general run of American population know anything about their family history except for the immediate members. By far the majority do not know the cause of death of their grandparents. Twenty-nine cancerous fraternities are selected as representative of our case-histories. Two generations only are represented in the majority, but in some of them three generations, and in one instance four generations. The normal members of the second and third generations are also given, so that the proportion of cancerous to non-cancerous individuals in two generations is exact. The majority of the cancerous

fraternities occur in small families, and in many cases the patient from whom the material examined came represented the end of the family line. In several instances all the members of the small family were cancerous. The charts explain themselves. The most striking thing shown, aside from the susceptibility of the family group, is the great prominence of tuberculosis as the most commonly associated disease of the cancer stock (Fig. 6). The two susceptibilities seem to run together, at least, in so far as our family histories are concerned. A tuberculous ancestry is not infrequently found in families where there is no family history of cancer back of the

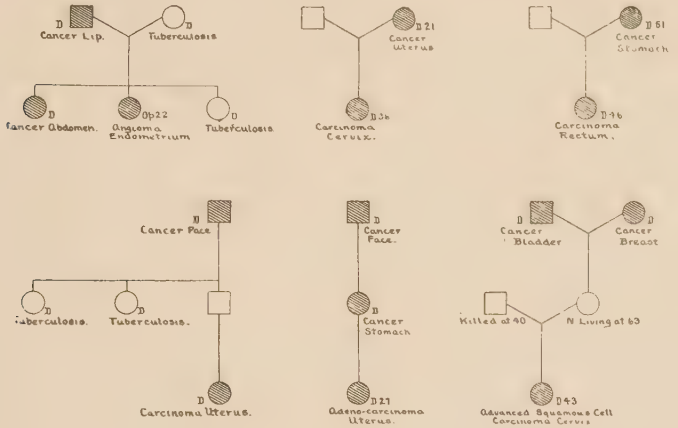

FIG. 5

present generation. Next to tuberculosis the most commonly associated disease with carcinoma is cardiac and renal disease (Figs. 7, 8, and 9).

It will be noted that the uterus, breast, gastro-intestinal tract and mouth are the parts of the body most frequently involved in the case of these family cancers. Cancer of the lip and rodent ulcer of the face show also a tendency to family occurrence.

In conclusion, the study of a large number of cases of carcinoma yields isolated but striking examples of a marked family occurrence through several generations; and a much more frequent family group or "cancerous fraternity" occurrence. From such histories it is hardly possible to draw any other conclusion than that a

definite cancer susceptibility exists in certain families. The great frequency of association with tuberculosis might be taken as an evidence of a general weakened resistance on the part of these

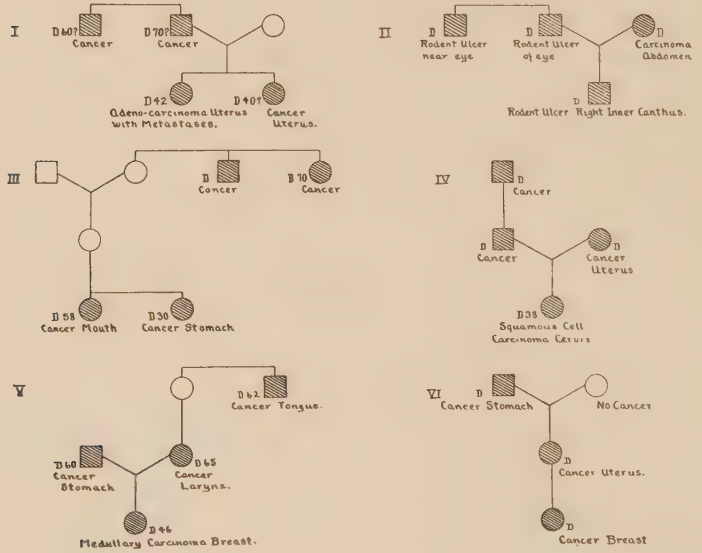

FIG. 6

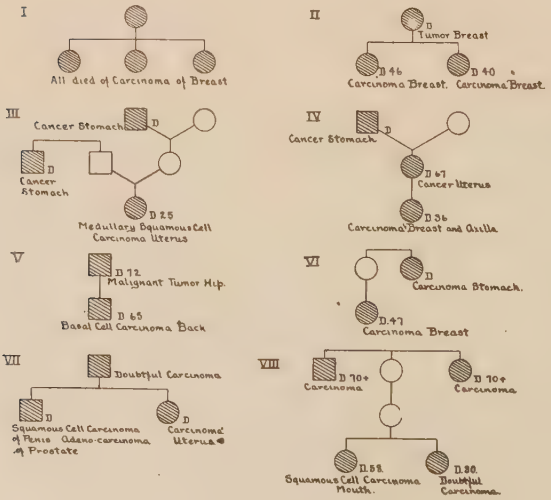

FIG. 7

family lines; and this conclusion is supported by the extinction of many of these lines through a lessened fertility.

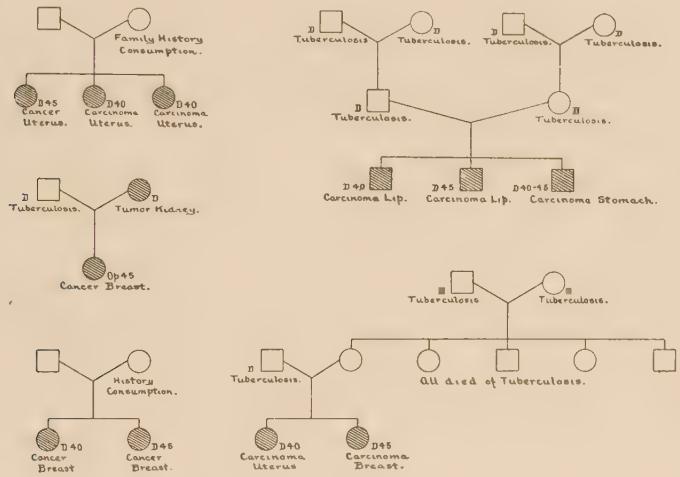

FIG. 8

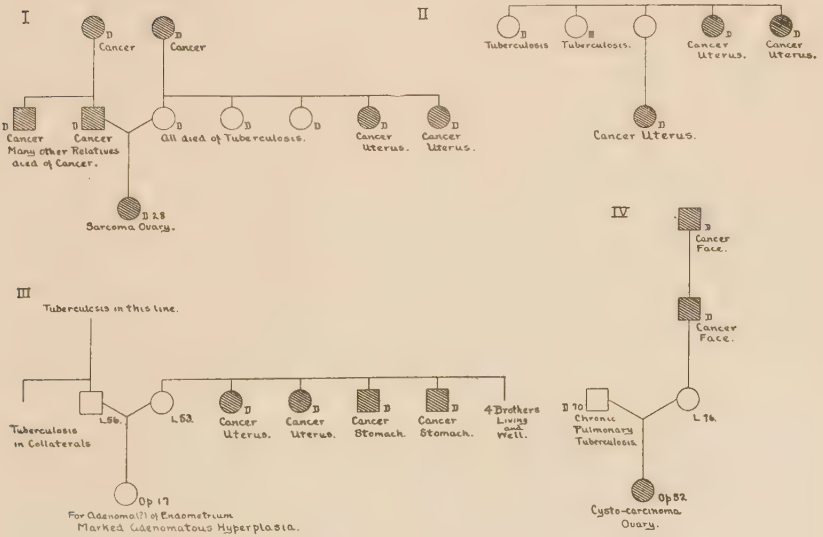

FIG. 9

In the study of all of our neoplasm material a family susceptibility is occasionally shown in the case of angioma, lymphangioma,

fibroma, neurofibroma, lipoma, myofibroma of uterus, adenoma of breast, and adenoma of thyroid; but extremely rarely in the case of sarcoma.

1. A marked susceptibility to carcinoma exists in the case of certain family generations and family groups.

2. This susceptibility is frequently associated with a marked susceptibility to tuberculosis, and also with reduced fertility.

3. The multiple occurrence of carcinoma in a family generation practically always means its occurrence in a preceding generation.

4. The family tendency is usually more marked when carcinoma occurs in both maternal and paternal lines.

5. Family susceptibility to carcinoma is shown particularly in the case of carcinoma of the mouth, lip, breast, stomach, intestines, and uterus.

6. In a family showing the occurrence of carcinoma in several generations there is a decided tendency for the neoplasm to develop at an earlier age in the members of the youngest generations. In this case the neoplasm often shows an increased malignancy.

7. Because of the difficulty of obtaining complete family records the laws of inheritance of carcinoma susceptibility cannot be determined accurately, and it is highly desirable that investigations of large family records should be made relative to the occurrence of carcinoma susceptibility. In Levin's study of cancerous fraternities in connection with the whole family history the percentage of the cancerous members in each cancerous fraternity corresponds very closely to the Mendelian percentage of members with recessive unit characters in a hybrid generation. The same conclusion might be drawn from my cases in certain instances, but it does not seem to me the data are sufficient for such conclusions. He himself does not consider this conclusion as final. Levin also concludes that resistance to cancer is a dominant character whose absence creates a susceptibility to cancer. While some of my cases show family history suggesting this, others would indicate a progressive degenerative inheritance—the running-out of a family line through the gradual development of an inferior stock, particularly so far as the resistance to tuberculosis and cancer is concerned.

Levin, as well as Williams (*The Natural History of Cancer,*

1908) noted the family tendency to specific localization of the cancer, particularly the uterus in the female members. This is well shown in my family histories and in some of the cancerous fraternities Levin concludes that the most important result of his investigation is the fact that it shows the presence of an inherited resistance to cancer growth. I would put it in just the opposite way and say that my observations are important in that they show in certain families an *inherited susceptibility* to cancer. If the majority of the human race do not show this susceptibility, *resistance to cancer* is a normal trait of the species. An *increased susceptibility* becomes, therefore, the abnormal character of importance, and our investigations should be carried along the line of attempting to determine just what lies back of this susceptibility.

MULTIPLE CONGENITAL OSTEOCHONDROMAS WITH DEGENERATION OF CRANIAL NERVES AND MUSCULAR DYSTROPHY

REPORT OF A CASE

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Congenital exostoses and enchondromas are among the rarer skeletal anomalies and have attracted much attention from the clinical observer and pathologist. The literature of the subject is voluminous and has been satisfactorily reviewed by others (Schmidt, Frangenheim). The writer will therefore limit himself to a brief statement of what is generally accepted as to the occurrence and histogenesis of the condition, with a description of a case with unusual associated features.

While very few observations on the newborn are recorded, such cases have been described by Murchison and Syme, Vix, Koester, Myers, and others. And there is much reason to accept the view that these tumors are truly congenital and due to abnormal *anlage* in the intermediary cartilages (von Bergmann).

The anomaly is, in many cases, clearly hereditary, and the heredity may be immediate from parent to child, or miss a generation. Likewise, an individual with exostosis may have descendants with enchondroma, or *vice versa*. Or, either type may show mixed heredity in the descendants. The incidence is greatly preponderant in the male members of such families.

The causes of the anomalous development are still obscure. Several authors have noted thyroid hypoplasia, cystic goitre, or Basedow's disease in their cases. Poor development of the mental

and sexual functions has also been remarked. Intermarriage of relatives has been suggested by some authors as a possible factor.

The exostoses are more common on the long bones, those of the lower extremities being more frequently involved than the bones of the arms. Small exostoses are often found on the ribs, especially near their heads. The feet and hands, as a rule, show few exostoses, while the pure enchondromas are most frequent on these parts. In general, the distribution of the growths is symmetrical, although exceptions occur in which one-half of the body, or one limb, is involved. The cranial bones of periosteal origin are free from this type of anomaly, but exostoses have been found at the sutures.

The characteristic deformities produced are: distortion and shortening of the long bones, with dwarfism, the trunk being better developed than the extremities. The sites of election for the tumors on the long bones are metaphysis, epiphysis, and diaphysis in order of frequency. The size of the exostoses varies from a few millimeters to many centimeters in diameter. In the forearm and leg the bones are often bridged by exostotic processes.

Bowing of the radius, with or without dislocation of the elbow, is quite frequent, due to the overgrowth of the radius stimulated by the tumor at the epiphysis. Bursæ at the outer portion of the tumors are common and may be large and contain floating bodies.

The cartilaginous covering of the exostoses is irregularly distributed and disappears during puberty, when growth of the tumor ceases. Later some absorption may take place; in a few instances the tumors have entirely disappeared. The structure, histologically, is very like that of normal bone. Primary necrosis and large areas of cystic degeneration are quite uncommon. Sarcomatous metamorphosis has been observed very rarely.

The tumors themselves are, for the most part, harmless, and they are not painful. But they may produce grave symptoms from pressure on contiguous bloodvessels and nerve trunks. The skin over the exostosis may become necrotic from pressure and lead to a severe local abscess or a general infection. In women the presence of exostoses in the pelvis may interfere with child-bearing. Exostoses may hamper the movement in important joints.

Very little is known of the association of other congenital anoma-

lies with exostosis. Several cases of extensive spinal cord lesions have been noted (Oberndorf), and some writers assert that anterior cell degeneration in the cord causes atrophic changes in the bones, leading to exostosis.

The patient, W. K., white, aged twenty-three years, single, teamster, was admitted to the City Hospital, July 20, 1912, complaining of weakness of the legs. On account of absolute deafness, the history was difficult to obtain and imperfect.

Family History. Father, who was killed in an accident, had "bony lumps" on both legs. Mother dead, cause unknown to patient. Three sisters and one brother living and well. None have any bone tumors or other congenital defect.

Past History. The patient does not remember any illness until present illness. Sisters say he was born with lumps on legs and arms, and while never very active, was healthy and able to work. At the time they last saw him, two years before admission, he was apparently well and not deaf.

He denies any venereal infection. Has always been thin and has worked as teamster until about eight months before admission, when his legs became too weak.

Present Illness. Legs have been weak for some time; he had to give up work about six or eight months ago. Did not feel sick. He does not know when deafness came on, but not more than a year or so ago. No pain or discharge from ears preceded or accompanied it. Says he can see as well as ever and that his legs are no worse.

Physical Examination. Medium-sized, under nourished man. Seems fairly bright and intelligent. Absolutely deaf, but can read the lips a little. Reads large print or writing very slowly and not altogether with full comprehension. Voice is low pitched, flat and husky; does not volunteer any remarks. Skin rather dry and rough, faint diffuse, brownish pigmentation.

Eyes: Deep set. Scleræ visible all around iris, giving a peculiar stare. Slight von Graefe. Winking normal. Movements of eyeballs normal. Pupils equal, react to light and accommodation. Fundi show clear-cut, pale disks with pallor more marked to temporal side. Veins and arteries small. No exudate or hemorrhages. Double optic atrophy of moderate grade. Visual fields show extreme general contraction to a small area about each fovea. No satisfactory color fields obtained.

Ears: Apparently absolutely deaf for air conduction. Cannot satisfactorily test for bone conduction, as patient does not understand what is wanted. No spontaneous nystagmus. After irrigation with cold water

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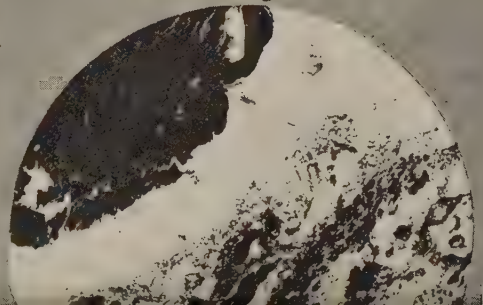

1-2-3. Photographs showing distribution of tumors.
4-5-6. Attitudes in rising from floor (dystrophic climbing).
7. Section of excised muscle showing atrophy.
8. Skull. Normal sella turcica.
9-16. Radiograms of skeleton.
11. Characteristic bowing of overgrown radius.
12. Large mass in the pelvic strait.
14. Tumor on left fibula showing cystic changes.

there is normal nystagmus response on both sides, showing that both vestibular nerves are intact. External ears and tympani apparently normal.

Nose, pharynx, tonsils, and larynx normal. No general or local glandular enlargement.

Thyroid: The neck is thin and the tracheal rings easily felt from the cricoid down below episternal notch, but no thyroid isthmus is palpable; lateral lobes cannot be made out.

Lungs: Slight impairment to percussion at both apices, generally enfeebled breath sounds, but no rales of any kind.

Heart: Normal in size and rhythm, no murmurs. Pulse good volume, regular, 70 to minute. No marked sclerosis. Systolic blood pressure 100 mm. (Tycos).

Abdomen rather scaphoid; no enlargement of liver or spleen. Colon seems rather full of pasty feces; large bony mass in left iliac fossa.

Genitalia normal. Hair normally developed over body.

The patient stands with legs wide apart, and walks with a steppage gait. When placed prone on the floor he gets up with difficulty, climbing up his legs like a dystrophic child. (See photographs.)

Musculature: Facial muscles and tongue normal. Considerable atrophy of shoulder girdle groups, and intrinsic muscles of hands. All the normal movements preserved. No fibrillation. Muscles of trunk seem small but normally active. Wasting of thigh and leg muscles on both sides, more marked on left. Extreme talipes equinus. There is marked weakness, but no paralysis. The peroneal and anterior tibial groups very much wasted. No fibrillation.

Electric Examination. Marked decrease in electric excitability without *qualitative* changes, *i. e.*, no reaction of degeneration. Suggests condition similar to dystrophy.

Sections of left tibialis anticus show marked atrophy with some hypertrophic fibers and supernucleation.

Nervous system, general; deep reflexes slightly exaggerated. Plantar response (Babinski) normal. No clonus. No sensory changes. No ataxia. No spasticity.

Bones: Skull small, but normally proportioned. Mandible normal. No exostosis made out.

Spine: No abnormalities made out, except that apparently there are six lumbar vertebræ and one less in sacrum.

Pelvis: Thickening of os pubis, huge exostosis projecting from left inner side of ilium. Clavicles thickened at inner ends. Scapulæ and ribs normal to palpation.

Arms: Upper third of both humeri much thickened and irregular. Large, irregular exostoses, size of a man's fist, project from inner aspect

at junction of upper and middle third. These are very hard, with small flaccid bursæ at outermost points of each, containing a few bean-sized bony, or calcareous, bodies. The lower ends of humeri seem normal. Exostoses on both ends of the forearm bones. Radii overgrown and bowed outward. Small spur on each first metacarpal. Some irregularity at bases of first phalanges. Other bones of wrists and hands normal.

Legs: Upper ends of femora much thickened, several spine-like outgrowths on each shaft. Tibiæ thickened at upper ends. The fibulæ show very large, bony tumors at the head, the left larger. These are irregular, firm, and no bursæ are felt. The bony masses, as large as an orange, contrast strangely with the atrophic legs. Exostoses are present about the malleoli on both sides. Marked talipes equinus, bilateral, but no large exostoses are felt on bones of the feet.

Urine: Faint trace of albumin and a few hyaline casts.

Blood: Red blood corpuscles, 6,400,000; hemoglobin, 90 per cent.; white blood corpuscles, 8300. Differential count shows normal formula. No anisocytosis. No abnormal constituents.

Wassermann reaction negative.

Spinal fluid: Pressure, 160 mm. (spinal fluid). Slightly turbid, 17 cells per c.mm. of small mononuclear type. Noguchi butyric acid test positive. Wassermann reaction negative.

Stools: No abnormal constituents.

X-ray Examination. Rarefaction of bones, with numerous exostoses of osteochondromatous type, symmetrically disposed on extremities and on pelvic bones. Heads of tibiæ suggest picture of osteitis. The largest tumor at the head of left fibula is apparently cystic. The skull seems entirely free from exostoses and the sella turcica is normal in size.

Summary. Young man with multiple congenital osteochondromas, (father similarly affected).

Thyroid atrophy. Later, development of degeneration in acoustic and optic nerves, and muscular dystrophy.

No cases with similar association of lesions have been found in searching the literature. The case probably represents congenital defects in the nervous systems, as well as in the bones. The *x*-ray of skull shows normal sella turcica and the escape of the vestibular nerves on both sides, while the acoustic nerves are completely degenerated, make it certain that the nerve changes cannot be due to pressure from exostoses. Whether the thyroid atrophy has any bearing on the bony or nervous changes cannot be more than suggested.

Special thanks are due to Dr. H. M. Thomas for his interest in the neurological examinations, to Dr. S. J. Crowe for his notes on the ears, nose, and larynx, and to Drs. F. H. Baetjer and Charles Waters for the numerous skiagrams.

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DISCUSSION

Dr. R. I. Cole: I should like to ask if there was any evidence of softening in any of the bones?

It is said that exostoses of this sort are apt to occur at the points of insertion of tendons.

Dr. Boggs: The appearance of rarefaction of the bones seen in the *x*-ray plates is not due to softening; it is due to a change in the structure of the bone produced by the disease.

An item of interest in the clinical study of this case was the fact that, though extremely emaciated, no thyroid gland could be made out even with the most careful palpation.

THE DIAGNOSIS OF ADHERENT PERICARDIUM AND THE OPERATION OF CARDIOLYSIS

By GEORGE DOCK, M.D.
ST. LOUIS

F. S., male, aged nineteen years, had diphtheria at four, but was otherwise well up to seven, when he had what was called bronchitis. After that he was short of breath, his abdomen became large and he had edema of the legs, worse in the evening, and sometimes edema of the face on waking in the morning. The edema became worse two years before admission, and tapping of the abdomen was resorted to three times within ten weeks and a milky fluid obtained. Recently he has been obliged to sit up to sleep. The patient says that he could, until recently, always reduce the edema by tennis playing.

On admission to Washington University Hospital, February 27, 1912, patient struck one's attention by his youthful appearance. He said he was usually taken for fifteen or sixteen years of age. He had no pubic or axillary hair. The frame was small and slender, but otherwise normal. The body was striking on account of a marked widening in the lower part of the thorax. There was extensive dulness in the left pleural cavity. The apex-beat could not be seen nor felt. The heart dulness extended 3 cm. beyond the sternum in the right fourth interspace. There was a faint systolic murmur at the apex region. Radial pulse 100; the radials and cervical vessels showed no anomalies at the first examination. The abdomen was distended (88 cm.), bulging in the flanks, and gave movable dulness with marked fluctuation. The liver could be felt 4 cm. below the costal margin and was exquisitely tender; the spleen not enlarged. The superficial abdominal veins were visible. Marked edema of feet, ankles, and scrotum.

Aspiration of the left pleura gave 1100 c.c. of watery, clear fluid, sp. gr. 1005, containing 2.2 gms. per liter of albumin (Tsuchiya). It contained a few lymphocytes and endothelial cells and very few polynuclears.

After this tapping the respiration was freer, the right edge of the heart dulness did not extend beyond the right sternal line.

Paracentesis of the abdomen gave 3 liters of slightly opalescent fluid, sp. gr. 1006, containing a few endothelial cells and lymphocytes, and 3 gms. per liter of albumin.

After tapping, the lower edge of the liver reached 10 cm. below the ribs. The surface felt uneven, the edge irregular. With the removal of the fluid it was possible to see a faint systolic retraction in the epigastrium; the liver moved down only 0.5 cm. on full inspiration; the heart moved only 1 cm. on changing from one side to the other. The neck vessels were distended and remained so in all phases of respiration.

The fluid reaccumulated in the pleura and abdomen and further tapping had to be resorted to, giving fluid of the same character as described.

Röntgenologic examination showed retraction of the right pleural cavity, with thickening on both sides, obscuring the heart.

In respiration only the upper part of the thorax moved very little upward, and without real expansion. The abdomen did not move in respiration.

The patient left the hospital and returned April 18, in about the same condition, but complaining of "thumping of the heart." The liver edge was still lower—13.5 cm. below the ribs. There was considerable fluid in the abdomen, and on suggesting tapping the patient left the hospital without permission. Efforts to get him to return were in vain. He moved his residence and we only learned his whereabouts after much searching, and only when he had been taken to the City Hospital, in bad condition. There he died Dec. 26, 1912, and through the kindness of Dr. O. H. Campbell, visiting physician, and Dr. D. L. Harris, pathologist, I was able to see the autopsy and to show the heart.

The autopsy showed in abstract: Ascites, peritoneum clear; liver very large, 1660 gms., surface finely nodular, yellowish red, hard. Dense adhesions of the right pleura with thickening up to 1 cm. in hard fibroid plates; less dense adhesions of left pleura with two sacs containing clear, yellowish fluid; the lung compressed; pericardium adherent all over, but sac not thickened; heart not enlarged; valves not altered; no extension of fibrous tissue into muscle; right auricle dilated; surrounded by dense connective tissue; both cavæ dilated. The right kidney showed enlarged calices filled with purulent material, the ureter dilated. There were a few gray miliary tubercles in various organs.

The patient was admitted with a diagnosis of multiple serositis, probably tuberculous. The fluid bore out the first part, but not the latter. I was struck by the features of mediastinitis, history of long-continued dyspnea, and edema without valvular disease or evidences of congenial lesion, delayed development, the large liver and limited respiratory expansion. Pericarditis, mediastinitis, and cirrhosis of the liver, possible Pick's syndrome, seemed probable. Demonstration of the pericardial involvement

was not at first easy, but some signs, not as widely known as they should be, enabled me to satisfy myself and my colleagues, though my efforts to put the diagnosis to practical value by an operation failed.

Many of the conventional signs of pericarditis were absent, such as prominence in the precordium, indulating impulse, retraction, Friedreich's sign. Though there was no distinct pulsus paradoxus, there was the pulse described by Wenckebach as being much more valuable as evidence of pericardial adhesions. While there was no visible systolic retraction, I was able, after removing the ascitic fluid to show retraction in a tracing, and my colleague, A. E. Taussig, made this plainer by the ingenious device of putting the patient across two chairs and taking a tracing upside down, as it were. We could also show the diastolic rebound of the ribs. With these signs and the characteristic respiration, to which Wenckebach has called attention, I explained the situation to the patient, and urged an operation expressing the hope that precisely because there was no proof of dense adhesions and none of enlargement of the heart, the separation of adhesions might do more good than in some more serious cases.

The operation of cardiolysis, proposed by L. Brauer in 1902, consists in the removal of the bony and cartilaginous wall of part of the thorax. The removal of dense adhesions may be included. In many cases patients have been greatly benefited, and in connection with this we must not think of operations for less serious diseases. Unoperated pericarditis and mediastinitis is always hopeless.

DISCUSSION

Dr. A. McPhedran: This report brings out a number of features I had not thought of and which I have never seen suggested; the effect of the respiratory movements upon the pulse, for example. I would concur in Dr. Dock's statement that the operation of cardiolysis is undeservedly neglected.

I have one case to submit in the hope of enlightenment: A young man, aged seventeen years, had had several attacks of rheumatism; after a period of overwork he was brought into the hospital with symptoms of an acute infection. There was noted during his stay in the hospital pericardial friction for one day; nothing else of note. The young man died and at the autopsy no material adhesions of the pericardium were found, only a few recent soft shreds; but there was evidence of an old mediastinitis with strong adhesions. The heart was very large, though it had suffered very little interference from adhesions, and there had been present only

an unimportant murmur. What had caused the great hypertrophy? Could it have been caused merely by beating within a resistant capsule?

Dr. Dock: Dr. McPhedran's observations on the case cited are important. The conditions described are often seen at autopsy, and it is frequently remarked that the adhesions present could not have sufficed to cause interference with the heart action; but there are many indications that the interference may be much greater than is apparent.

THE TREATMENT OF SYPHILITIC AFFECTIONS OF THE CENTRAL NERVOUS SYSTEM, WITH SPECIAL REFERENCE TO THE USE OF INTRASPINOUS INJECTIONS

By HOMER F. SWIFT, M.D., and ARTHUR W. M. ELLIS, M.B.

(From the Hospital of the Rockefeller Institute for Medical Research, New York)

Syphilis of the central nervous system is a manifestation of an infectious disease caused by a known parasite, against which we have at least two specific therapeutic agents. It is therefore amenable to treatment. The problems to be solved are (1) how to recognize the condition before irreparable damage has been done to important structures; (2) the determination of the most efficient methods of application of our curative agents. The first can be solved only by careful clinical study and routine examination of the cerebrospinal fluid of all suspected patients. It is the purpose of this communication to present the results of an attempt to solve the second problem, viz., the determination of the best method of application of the curative agents.

The demonstration of the Treponema pallidum in general paralysis has definitely established the fact that in the so-called parasyphilitic nervous diseases there is active syphilis of the central nervous system. The cerebrospinal fluid in paresis and tabes shows qualitatively the same alterations as does the fluid in cerebrospinal syphilis. The usual changes occurring in the cerebrospinal fluid in these conditions are pleocytosis, with a predominance of mononuclear forms, and an increase in globulin. These abnormalities indicate the presence of a chronic inflammatory process in the cerebrospinal axis. A positive Wassermann reaction in the fluid indicates that the inflammation is syphilitic in nature. These

abnormal constituents usually disappear more rapidly under specific treatment in involvement of the nervous system occurring early than they do in such lesions occurring late in syphilis or in tabes or general paralysis, especially the latter. In late syphilis the spirochetes have established themselves in strongholds difficult to reach with drugs. Such strongholds are the regions of poor vascularization, and in these the central nervous system is particularly rich. The Treponema pallidum has a predilection for lymph spaces. For practical purposes the perivascular lymphatics and the perineuronal spaces may be considered as lymph spaces which are not in direct communication with the general lymphatic system, but which are part of the subarachnoid space. Through them flows the cerebrospinal fluid. It has been well established that there is very little excretion of curative agents from the blood into the cerebrospinal fluid. Flexner and his co-workers have shown the necessity of directly introducing the therapeutic sera into the subarachnoid space in the various forms of purulent meningitis. The same principle no doubt holds true, to a considerable degree, in all forms of meningitis.

In dealing with syphilis of the central nervous system, we are, however, more fortunate than is the case in purulent meningitis for here the introduction of our therapeutic agents into the general circulation is of undoubted benefit. With mercury and iodides and with salvarsan intravenously much can be done, and in many patients all clinical signs and symptoms can be relieved. Efficient therapy, however, means more than the relief of symptoms; it involves also the eradication of all evidence of disease. This is more difficult. The changes occurring in the cerebrospinal fluid—pleocytosis, increased globulin, and positive Wassermann reaction—must, as has been stated, be looked upon as evidence of active syphilis of the central nervous system. No treatment can be considered adequate which does not result in the permanent disappearance of these abnormalities.

While rapid symptomatic improvement frequently follows the use of mercury and iodides, the relatively slight influence of these drugs on the abnormal constituents in the spinal fluid suggests at once the probability of subsequent relapse. In tabes the use

of mercury seems frequently to actually increase the intensity of symptoms. Salvarsan intravenously acts more rapidly than mercury, especially in reducing the degree of pleocytosis. To cause a disappearance of the increased globulin and to change the Wassermann reaction from positive to negative is, however, much more difficult.

The idea of intensifying the treatment of syphilis of the central nervous system by the introduction of salvarsan directly into the cerebrospinal fluid naturally suggests itself. To determine whether this might be safely done, we injected high dilutions of the drug in monkey serum intraspinously into monkeys. Subsequent examination of the cerebrospinal fluid showed that the drug introduced in this form was too irritating to warrant its application to patients. Neosalvarsan injected intraspinously into monkeys was less irritating, but when injected into patients produced symptoms too severe to warrant its continued use.[1] On the contrary, serum can be repeatedly injected into the subarachnoid space without demonstrable injury to the nervous tissue.

The blood serum of patient's treated intravenously with salvarsan has been shown to have definite therapeutic value when injected subcutaneously into patients with congenital and secondary syphilis. We have been able to show that this serum exerts a spirocheticidal action on the spirochetes of relapsing fever.[2] When the serum is

[1] Wechselmann (Deutsch. med. Woch., 1912, xxxviii, 1446) reports that he had injected neosalvarsan intraspinously into two patients with general paralysis and into two children with congenital lues, without any injurious effects. Marinesco (Zeitschr. f. physik. u. diätet. Therap., 1913, xvii, 194) reports the results in thirteen patients, each of whom received 5 mg. neosalvarsan in 4 c.c. solution intraspinously. In ten of these severe unpleasant symptoms immediately appeared. Eight of them had permanent bladder disturbance. From his experience Marinesco advises strongly against the intraspinous injection of neosalvarsan. We are in complete accord with his conclusions. In the same communication Marinesco states that he had treated patients with syphilis of the central nervous system with serum obtained from patients with secondary syphilis after treatment with salvarsan. There were some beneficial results, but the work was not continued. Robertson (Edinburgh Med. Jour., 1913, x, 428) reports on the intraspinous treatment of patients with general paralysis. For this treatment he used the serum of patients with secondary syphilis, which was withdrawn on the third day after a salvarsan injection, and also the paretic's own serum, withdrawn one hour after the intravenous injection of salvarsan. Only a few treatments were given to each patient, but half of those treated showed some improvement.

[2] R. Gonder (Zeitschr. f. Immunitätsforsch., Orig., 1912, xv, 257) reports on a similar spirocheticidal action of the blood of salvarsan treated rats on the spirochetes of relapsing fever.

allowed to act on the spirochetes *in vitro* and subsequently these are injected into mice, they do not develop in the mice as do untreated spirochetes or spirochetes on which normal serum has been allowed to act. Heating the serum to 56° C. increases the spirocheticidal action. We have also used the serum of syphilitic patients to make serum agar for the growth of Treponema pallidum after Noguchi's method. Cultures in media made with serum obtained before treatment grew practically as well as in that made with normal serum, while in media made with serum obtained an hour after intravenous injections of salvarsan the spirochetes grew more slowly or not at all. In media made with serum which was obtained at longer intervals after treatment the growth approximated that in normal control tubes. These experiments indicate that the serum has the greatest inhibitory effect shortly after the injection of salvarsan.

All of the above-mentioned experiments support the view that the serum of salvarsan treated patients has a definite antispirocheticidal effect both *in vitro* and *in vivo*. Such sera are ideal preparations for direct introduction into the subarachnoid space, and for the past two years we have been studying the results of the injection of such sera intraspinously into patients with syphilitic disease of the central nervous system.

The technique that we have employed varies but little from that previously described,[1] and is as follows: One hour after the intravenous injection of salvarsan 40 c.c. of blood is withdrawn directly into bottle-shaped centrifuge tubes, and allowed to coagulate, after which it is centrifugalized. The following day 12 c.c. of serum is pipetted off and diluted with 18 c.c. of normal saline. This 40 per cent. serum[2] is then heated at 56° C. for one-half hour. After lumbar puncture the cerebrospinal fluid is withdrawn until the pressure is reduced to 30 mm., cerebrospinal fluid pressure. The barrel of a 20 c.c. Luer syringe (which has a capacity of about 30 c.c.) is connected to the needle by means of a rubber tube about 40 cm. long. The tubing is then allowed to fill with cerebrospinal

[1] H. F. Swift and A. W. M. Ellis, New York Med. Jour., 1912, xcvi, 53.

[2] In patients who do not have reactions following the injection of 40 per cent. serum the strength is at times increased to 50 or 60 per cent., or even stronger.

fluid so that no air will be injected. The serum is then poured into the syringe and allowed to flow slowly into the subarachnoid space by means of gravity. At times it is necessary to insert the plunger of the syringe to inject the last 5 c.c. of fluid. It is important that the larger part of the serum should be injected by gravity, and if the rubber tubing is not more than 40 cm. long the pressure cannot be higher than 400 mm. Usually the serum flows in easily under even a lower pressure. By the gravity method the danger of suddenly increasing the intraspinous pressure to the danger point, such as might occur with rapid injection with a syringe, is avoided. Frequently there is a certain amount of pain in the legs commencing a few hours after the injection. The pain is more often noticed in tabetics than in patients with cerebrospinal syphilis. It can usually be controlled by means of phenacetin and codeine. Occasionally morphine is required.

The therapeutic effect of this form of treatment is illustrated in the tables, where the treatment, Wassermann reaction in the blood and in the cerebrospinal fluid, the cell count and globulin in the fluid of each patient are given. In some of the tables the Wassermann reaction in the cerebrospinal fluid is indicated with two different antigens. Prior to January, 1913, fetal liver extract was used as antigen. It was then found that an alcoholic extract of human heart, to which 0.4 per cent. cholesterin had been added, was a much more sensitive reagent. In order not to confuse the results it was considered wise to continue the use of the liver antigen in those cases where it had previously been used, and to add the comparative reactions with the cholesterin-heart antigen. Unless otherwise designated in the notes after January, 1913, a completely negative reaction indicates that it was negative with the cholesterin-heart as well as with the liver antigen. In the cerebrospinal fluid column, the amount of fluid which gave complete fixation is indicated.[1] The quantitative titration of the strength of reaction has been used since November, 1911. Previous to that time only

[1] In performing the reaction with the cerebrospinal fluid 0.5 c.c., 0.4 c.c., 0.3 c.c., 0.2 c.c., 0.1 c.c., and 0.05 c.c. fluid are used. As we employ one-half quantities of all the reagents as compared with the amounts originally recommended for the Wassermann reaction, these quantities therefore correspond to 1.0 c.c., 0.8 c.c., 0.6 c.c., 0.4 c.c., 0.2 c.c., and 0.1 c.c. respectively.

0.1 c.c. of fluid was used. The titration of the strength of the reaction furnishes a fair index of the effect of treatment. In this report we wish to lay more emphasis on the improvement in the condition of the cerebrospinal fluid than upon the clinical improvement, because it is entirely objective and probably gives us a better idea of the actual effect of our therapeutic measures.

CASE 85.—C. L. V., a well-marked tabetic, who had symptoms for about six years, lately becoming more marked. He had lightning pains, difficulty in walking, girdle sensation about the abdomen, and Charcot joint in the right hip. He had received practically no antisyphilitic treatment prior

TABLE I.—No. 85, C. L. V. aged thirty-five years; tabes dorsalis, six years; syphilis, sixteen years. Result: Improved.

	Blood.	Cerebrospinal Fluid.			Treatment.	
Date.	Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Wassermann reaction.	Intravenous.	Intraspinous serum.
Nov.10,1910,to	++	..	....	....	16 injections HgCl,	
Jan. 10, 1911	+	..	....	....	intramuscularly.	
Jan. 16	±	125	++	0.1 c.c. –	Salvarsan 0.2 gm.	
Jan. 25	+	..	....	....	Salvarsan 0.3 gm.	
Feb. 8	+	..	....	....	Salvarsan 0.36 gm.	
Feb. 13	....	150	±	0.1 c.c. –		
Feb. 15 to	±	..	....	....	Mixed	
Aug. 20	....	..	....	....	treatment	
Aug. 21	±	63	+	0.1 c.c.± ?		
Aug. 26 to	....	..	....	....	Salvarsan	
Sept. 22	± ?	..	....	....	5 x 0.2 gm.	
Sept. 22	....	26	±	0.1 c.c. –		
Nov. 24	....	..	....	....	Salvarsan 0.2 gm.	
Dec. 1[1]	± ?	50	+	0.5 c.c.±	Salvarsan 0.2 gm.	18 c.c. of 50%
Dec. 11	±	20	+	....	Salvarsan 0.2 gm.	30 c.c. of 50%
Dec. 18	±	20	±	0.5 c.c.±	Salvarsan 0.2 gm.	20 c.c. of 40%
1912						
Jan. 5	–	12	±	0.5 c.c.+±	Salvarsan 0.3 gm.	30 c.c. of 40%
Jan. 12	–	4	–	0.5 c.c.±	Salvarsan 0.3 gm.	30 c.c. of 50%
Jan. 15	–	..	....	....	Salvarsan 0.2 gm.	
Jan. 20	....	5	–	0.5 c.c.± ?		
July 9	–	2	–	0.5 c.c. –		
Sept. 10	–	1	–	0.5 c.c. –		
1913						
May 15	–	3	–	0.5 c.c. –		

to November, 1910. In the first year of treatment he received sixteen intramuscular injections of bichloride of mercury, nine intravenous injections of salvarsan, a total of 2 gm., and six months' mixed treatment by mouth. The result of this was to reduce the pleocytosis from 125 to 50

[1] Where both intravenous and intraspinous treatment were used the date of the intravenous injection is indicated. The intraspinous injection was given on the following day.

per c.mm. The effect on the Wassermann reaction in the cerebrospinal fluid was not determined, because an insufficient quantity of fluid was employed. After the institution of intraspinous treatment with his own serum, the fluid became normal in six weeks. During this period a total of 1.4 gm. salvarsan was given in six intravenous injections and five intraspinous injections, a total of 60 c.c. of undiluted serum.[1] For over a year the fluid has remained normal and the patient has been practically free from pain. The Charcot joint has prohibited his return to his usual work, although he goes about very well. There has been no advance in his tabes.

Case 213.—O. W. A. had a rapidly progressing tabes of two and one-half years' duration. The most marked symptoms were ataxia, pain,

Table II.—No. 213, O. W. A., aged twenty-nine years; tabes dorsalis, two and one-half years; syphilis, nine years. Result: Improved.

		Cerebrospinal Fluid.					
				Wassermann reaction.		Treatment.	
Date 1911.	Blood. Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Liver antigen.	Cholesterin. heart antigen.	Intravenous.	Intraspinous serum.
June 23 to	++	..	....	.....	.....	Salvarsan	
Aug. 2	++	..	....	.....	.....	5 x 0.2 gm.	
Aug. 5	....	110	—	0.1 c.c.±			
Aug. 10 to	++	..	....	.....	.....	Salvarsan	
Oct. 20	+	..	....	.....	.....	4 x 0.2 gm.	
Oct. 27	+	75	—	0.1 c.c.++	.....	Salvarsan 0.2 gm.	25 c.c. of 40%
Nov. 3	++	..	....	.....	.....	Salvarsan 0.2 gm.	
Nov. 21	++	..	....	0.1 c.c.++	.....	Salvarsan 0.2 gm.	20 c.c. of 50%
Dec. 12	++	20	±	0.1 c.c.++	.....	Salvarsan 0.2 gm.	30 c.c. of 70%
Dec. 19	++	19	±	0.2 c.c.++	.....	Salvarsan 0.2 gm.	25 c.c. of 40%
1912							
Jan. 5	+	22	—	0.1 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 50%
Jan. 12	+	8	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 50%
Jan. 19	+	10	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 50%
Jan. 25	+±	8	—	0.2 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 50%
Feb. 1	....	5	—	.....	.....	Salvarsan 0.3 gm.	25 c.c. of 40%
Feb. 8	++	7	—	0.2 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 50%
April 11	+	2	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 40%
April 18	±	..	....	.....	.....	Salvarsan 0.3 gm.	
April 25	++	10	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 40%
May 2	++	8	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 40%
May 16	+	10	—	0.3 c.c.++	.....	Salvarsan 0.3 gm.	30 c.c. of 40%
1913							
Feb. 22	++	1	—	0.4 c.c.++	0.3 c.c.++	Neosal. 0.75 gm.	30 c.c. of 40%

and hyperesthesia in the lumbar region. In the first four months of treatment a total of 1.8 gm. of salvarsan was given in nine intravenous injections, which produced a drop in cells from 125 to 75, but had no effect on

[1] In the tables the amount of diluted serum which was injected at each treatment is shown, while in abstracts in the text the total amount of undiluted serum is given.

the Wassermann reaction in the cerebrospinal fluid. Upon the institution of intraspinous injection of patient's own serum, there was an immediate drop in the number of cells. In the next seven months he received 4.3 gm. salvarsan in sixteen intravenous injections and fourteen intraspinous injections, a total of 184 c.c. of serum. Under this treatment the cells were reduced to practically normal in number, and the Wassermann reaction in the cerebrospinal fluid was much reduced in strength. Because the patient felt so much better he neglected to report for nine months, during which time the fluid remained practically the same.

A marked beneficial effect was noted in both of these patients when the intraspinous treatment was instituted, but the objection might be advanced that the improvement was due to the continuation of the salvarsan intravenously. To determine the effect of the intraspinous treatment alone, several patients were treated intraspinously with the serum from other patients who had received intravenous injections of salvarsan.

Case 557.—C. H. L., a man, aged fifty years, with fairly well-marked tabes dating back ten years since the onset. He had had marked gastric

Table III.—No 557, C. H. L.; aged fifty-two years; tabes dorsalis, ten years; syphilis, thirty years. Result: Improved.

	Blood.	Cerebrospinal Fluid.			Treatment.	
Date 1911.	Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Wassermann reaction.	Intravenous.	Intraspinous other patients' serum.
Oct. 25	−	42	++	0.1 c.c. ++		
Oct. 30	....	41	++	0.1 c.c. ++	.....	25 c.c. of 40%
Nov. 6	....	40	++	0.1 c.c. ++	.....	20 c.c. of 40%
Nov. 18	....	50	++	0.2 c.c. ++	.....	22 c.c. of 40%
Dec. 3	−	18	++	0.2 c.c. ++	.....	26 c.c. of 50%
Dec. 12	....	17	++	0.1 c.c. ++	.....	30 c.c. of 50%
Dec. 28	....	15	++	0.4 c.c. ++	.....	25 c.c. of 40%
1912						
Jan. 6	....	15	+	0.1 c.c. ++	.....	25 c.c. of 40%
Jan. 12	....	10	++	0.2 c.c. ++	.....	30 c.c. of 50%
Jan. 23	....	14	++	0.5 c.c. ± ?	.....	26 c.c. of 50%
Jan. 31	....	16	+	0.5 c.c. ±	.....	30 c.c. of 50%
Feb. 7	....	17	+	0.5 c.c. +±	.....	30 c.c. of 50%
March 4	−	15	+	0.5 c.c. +±		
April 10	....	10	±	0.5 c.c. ±		
April 16 to	−	..	....	....	Salvarsan	
May 14	−	..	....	....	5 x 0.3 gm.	
May 14	....	19	+	0.5 c.c. ±		
Sept. 24	−	8	+	0.5 c.c. −		
1913						
March 28	−	5	−	0.5 c.c. −		

disturbances for the past three years, so that he had lost much weight and had been incapacitated for several months. In three and one-half months he received eleven intraspinous injections, a total of 130 c.c. undiluted serum, which was obtained from other patients. This treatment resulted in the reduction of all the abnormal constituents in the fluid nearly to normal. Then 1.5 gram salvarsan in five intravenous injections was given with practically no effect on the fluid. The patient was so much improved that he returned to work and received no further treatment. At the time of the last examination of the fluid, nearly one year after treatment was discontinued, his spinal fluid was entirely normal. The tabetic process has shown practically no advance since the treatment was started.

Case 675.—H. G. G., a man, aged forty-two years, who had well-marked tabes of two and one-half years' duration. He had never received any antisyphilitic treatment previous to his admission. In five and one-half months he was given ten intraspinous injections, a total of 120 c.c. of undiluted serum. After eight treatments the cerebrospinal fluid was

Table IV.—No. 675, H. G. G., aged forty-two years; tabes dorsalis, two and one-half years; syphilis denied. Result: Improved.

	Blood.	Cerebrospinal Fluid.			Treatment.
Date 1912.	Wassermann reaction.	Cells.	Noguchi globulin.	Wassermann reaction.	Intraspinous other patient's serum.
March 18	±	35	±	0.3 c.c. ++	
May 2	−				
May 5	....	41	+	0.3 c.c. ++	30 c.c. of 40%
May 14	....	24	±	0.4 c.c. ++	30 c.c. of 40%
May 21	....	17	±	0.4 c.c. ++	30 c.c. of 40%
June 10	−				
June 20	....	14	±	0.5 c.c. ++	30 c.c. of 40%
June 27	....	33	±	0.5 c.c. ++	30 c.c. of 40%
July 9	....	12	±	0.5 c.c. ++	30 c.c. of 40%
July 21	....	35	+	0.5 c.c. ++	30 c.c. of 40%
July 30	−				
Sept. 19	....	14	−	0.5 c.c. ±	30 c.c. of 40%
Oct. 1	....	8	−	0.5 c.c. −	30 c.c. of 40%
Oct. 19	....	7	−	0.5 c.c. −	30 c.c. of 40%
1913					
Jan. 5	−	5	−	0.5 c.c. −	

January 5, died of lobar pneumonia; autopsy showed typical tabes.

normal. About three months after his last treatment he died of lobar pneumonia. The cerebrospinal fluid taken immediately after death was normal. Autopsy revealed changes in the cord typical of tabes dorsalis. The symptomatic improvement, as well as the return to normal of the cerebrospinal fluid, were most striking.

Case 565.—V. H., a man, aged forty-two years, who had pains referable to dorsal root irritation for three years. One year before admission he had received two intravenous injections of salvarsan followed by a course of mercury inunctions and considerable KI by mouth. Before this treatment was started he had 94 cells per cmm. in the cerebrospinal fluid. Our

Table V.—No. 565, V. H., aged forty-two years; teritary syphilitic meningitis (radiculitis); syphilis, nine years ago.

Date 1912.	Blood. Wassermann reaction.	Cerebrospinal Fluid. Cells.	Noguchi globulin.	Wassermann reaction.	Treatment. Intraspinous other patient's serum.
April 5	+±	124	++	0.1 c.c. ++	
April 10	....	64	++	0.1 c.c. +±	30 c.c. 40%
April 19	....	17	+	0.2 c.c. ++	30 c.c. 40%
April 28	....	30	+	0.2 c.c. ++	30 c.c. of 40%
May 7	....	23	+	0.2 c.c. ++	30 c.c. of 40%
Sept. 12 [1]	....	4	−	Negative.	

first examination showed 124 cells, a heavy globulin, and a strongly positive Wassermann reaction. He then had 48 c.c. of serum in four intraspinous injections. Four months later he was examined in another hospital and his spinal fluid reported as normal. Unfortunately, the patient would not continue under observation. The symptomatic improvement was less marked than the improvement in the pathological cerebrospinal fluid.

These three cases illustrate very well that definite and marked change in the condition of the cerebrospinal fluid can be brought about by the intraspinous injection of serum alone, since none of these last three patients had had any other form of treatment. As there is also a definite effect from intravenous injection of salvarsan, it would seem that the combination of these two forms of treatment would produce a more rapid effect than either alone. This is well illustrated by the next three cases.

Case 485.—C. M., a man, aged forty-eight years, with moderately advanced tabes of two years' duration. He had transient diplopia seven years ago. In eight months patient was given 3.3 grams salvarsan in eleven intravenous injections, and nine intraspinous injections, a total of 109 c.c. of his own serum. After the fourth intraspinous treatment the fluid was practically normal except for a moderate increase in globulin, which has persisted up to the present time.

[1] Report furnished by Neurological Institute.

TABLE VI.—No. 485, C. M., aged forty-eight years; tabes dorsalis, one and one-half years; syphilis, nineteen years.

	Blood.	Cerebrospinal Fluid.			Treatment.	
Date 1912.	Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Wassermann reaction.	Intravenous.	Intraspinous serum.
Jan. 26	—	130	++	0.5 c.c. ++		
Jan. 30	—	90	++	0.5 c.c. +	Salvarsan 0.2 gm.	30 c.c. of 50%
Feb. 6	—	40	++	0.5 c.c. ±	Salvarsan 0.3 gm.	
Feb. 13	—	26	++	0.5 c.c. —	Salvarsan 0.3 gm.	25 c.c. of 40%
Feb. 20	—	24	++	0.5 c.c. —	Salvarsan 0.3 gm.	30 c.c. of 40%
April 3	—	9	+	0.5 c.c. —	Salvarsan 0.3 gm.	20 c.c. of 40%
April 17	—	..	....	....	Salvarsan 0.3 gm.	
May 6	—	6	+	0.5 c.c. —	Salvarsan 0.3 gm.	30 c.c. of 40%
June 20	—	8	+	0.5 c.c. —	Salvarsan 0.3 gm.	30 c.c. of 40%
July 18	—	4	±	0.5 c.c. —	Salvarsan 0.3 gm.	30 c.c. of 40%
Aug 15	—	4	±	0.5 c.c. ± ?	Salvarsan 0.3 gm.	30 c.c. of 40%
Sept. 12	—	2	±	0.5 c.c. ± ?	Salvarsan 0.4 gm.	30 c.c. of 40%
Oct. 29	—	..	....	....	Neosalvarsan 0.9 gm.	
Nov. 19	—	4	+	0.5 c.c. —		
Dec. 17	—	..	....	....	Neosalvarsan 0.9 gm.	
				Cholesterin-heart		
1913				antigen.		
April 9	—	3	+	0.5 c.c. —	Salvarsan 0.5 gm.	

CASE 893.—F. B., a man, aged thirty-four years, who had early tabes, suffering chiefly from shooting pain in the legs for two years, and slight

TABLE VII.—No. 893, F. B., aged thirty-four years; tabes dorsalis, two years; syphilis, thirteen years. Result: Improved.

	Blood.	Cerebrospinal Fluid.			Treatment.	
Date. 1912	Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Wassermann reaction.	Intravenous.	Intraspinous serum.
Oct. 18	+	40	±	0.5 c.c. +	Neosalvarsan 0.75 gm.	
Oct. 28	++	..	....	....	Neosalvarsan 0.45 gm.	
Nov. 2	....	57	+	0.5 c.c. +±		
Nov. 4	++	47	+	0.5 c.c. ++	Neosalvarsan 0.90 gm.	30 c.c. of 40%
Nov. 12	....	13	+	0.5 c.c. —	Neosalvarsan 0.90 gm.	30 c.c. of 40%
Nov. 18	....	..	....	....	Neosalvarsan 0.90 gm.	
Nov. 25	++	..	....	....	Neosalvarsan 0.90 gm.	
Dec. 2	++	10	+	0.5 c.c. —	Neosalvarsan 0.90 gm.	30 c.c. of 40%
Dec. 16	....	..	....	....	Neosalvarsan 0.90 gm.	
Dec. 17	....	2	±	0.5 c.c. —		
	Cholesterin-heart			Cholesterin-heart		
1913	antigen.			antigen.		
Jan. 25	....	7	±	0.5 c.c. —		
Feb. 8	++	5	±	0.5 c.c. —	Neosalvarsan 0.90 gm.	30 c.c. of 40%
March 14	++	..	....	....	Neosalvarsan 0.75 gm.	
Mar. 28 to	++	..	....	....	Salvarsan	
April 25	++	..	....	....	3 x 0.50 gm.	
April 25	++	3	±	0.5 c.c. —		

unsteadiness in gait for six months. In four months he received 8.2 gram. neosalvarsan and four intraspinous injections, a total of 48 c.c. of his own serum. The increase in the intensity of the Wassermann reaction after

the treatment was started is worthy of note. The sudden drop in cells and the disappearance of the Wassermann reaction occurred after the first intraspinous injection. After the fluid was reduced to normal except for a slight increase in globulin, the treatment was continued intravenously because of the persistence of the Wassermann reaction in the blood-serum. This case illustrates the point which we have noticed that if before treatment was started large quantities of the fluid are required to obtain a positive Wassermann reaction, the reaction disappears fairly rapidly under treatment.

Case 605.—F. K., a man, aged twenty-seven years, who was admitted because of ophthalmoplegia interna of the left eye. He denied syphilis and had not taken antisyphilitic treatment. His physical examination was normal except for one dilated pupil. In one year he received twenty intravenous injections, a total of 6 grams of salvarsan and 3.6 grams neo-

Table VIII.—No. 605, F. K.,aged twenty-seven years; cerebrospinal syphilis; duration?; previous treatment 0. Result: Improved.

	Blood.	Cerebrospinal Fluid.			Treatment.		
Date. 1912	Wassermann reaction.	Cells.	Noguchi globulin.	Wassermann reaction.	Intravenous.		Intraspinous serum.
April 25	++	59	+	0.2 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
May 2	++	..	....	0.3 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
May 9	+	..	....	....	Salvarsan	0.3 gm.	
May 23	+	14	+	0.3 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
June 13	+	5	±	0.3 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
June 20	+	6	±	0.4 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
July 18	±	2	±	0.5 c.c. ++	Salvarsan	0.3 g.m	30 c.c. of 40%
July 26	....	..	....	....	Salvarsan	0.3 gm.	
Aug. 15	±	2	±	0.4 c.c. ++	Salvarsan	0.3 gm.	30 c.c. of 40%
Sept. 12	±	6	±	0.4 c.c. ++	Salvarsan	0.4 gm.	30 c.c. of 40%
Oct. 3	±	..	....	....	Salvarsan 2 x	0.3 gm.	
Oct. 17	−	..	....	....	Salvarsan	0.6 gm.	
Nov. 2	....	7	−	0.5 c.c. ++			
Nov. 22	+	..	....	....	Salvarsan	0.6 gm.	
Dec. 12	−	8	−	0.5 c.c. ++	Neosalvarsan	0.9 gm.	
1913	Cholesterin-heart antigen.			Cholesterin-heart antigen.			
Jan. 3	++	4	−	0.5 c.c. ++	Neosalvarsan	0.9 gm.	30 c.c. of 40%
Jan. 31	++	3	−	0.5 c.c. +±	Neosalvarsan	0.9 gm.	30 c.c. of 40%
Feb. 28	+±	4	−	0.5 c.c. +	Neosalvarsan	0.9 gm.	30 c.c. of 40%
April 4	+±	..	....	....	Salvarsan	0.6 gm.	
April 25	+	2	± ?	0.5 c.c. −	Salvarsan	0.5 gm.	30 c.c. of 40%

salvarsan, and 144 c.c. of his own serum in twelve intraspinous injections. At the end of this time the cerebrospinal fluid became normal and there was a distinct diminution in the intensity of the Wassermann reaction in the blood-serum. This is the type of case which Nonne and Erb have described as usually going on to tabes or paresis. The distinct changes which

were first found in the cerebrospinal fluid indicate that the patient was suffering from an active syphilis of the central nervous system, although he presented as physical signs only one dilated pupil. It seems reasonable to suppose that the treatment with the resulting return to normal of the cerebrospinal fluid has resulted in an arrest of the syphilitic process. Probably by careful clinical examination, as well as examination of the cerebrospinal fluids, many cases of tabes could be detected in this early stage and arrested by applying intensive and prolonged treatment. It is worthy of note that many of the tabetics give a history of diplopia or other transient eye disturbances several years before the onset of any other symptoms. It is important to recognize the disease in this early stage in order that it may not be allowed to progress until marked nerve degeneration has occurred.

TABLE IX.—No. 152, O. F., aged thirty-two years; tabes dorsalis, three and one-half years; syphilis, ten years. Result: Improvement, relapse, improvement.

		Cerebrospinal fluid.					
				Wassermann reaction.		Treatment.	
Date. 1911.	Blood. Wassermann reaction.	Cells per cmm.	Noguchi globulin	Liver antigen.	Cholesterin-heart antigen.	Intravenous.	Intraspinous serum.
April 4 to	++	27	++	0.1 c.c. −	.....	Salvarsan	
May 18	+	..	....	.....	.....	5 x 0.20 gm.	
May 19	....	39	++	0.1 c.c. +	.....		
Oct. 13	+	..	....	.....	.....	Salvarsan 0.20 gm.	
Oct. 20	±	9	+	0.1 c.c. ±	.....	Salvarsan 0.20 gm.	17 c.c. of 40%
Oct. 27 to	....	..	....	.....	.....	Salvarsan	
Nov. 17	....	..	....	.....	.....	4 x 0.20 gm.	
Nov. 20 1912	....	10	+				
April 9	−	14	±	0.2 c.c. ++	.....	Salvarsan 0.30 gm.	30 c.c. of 40%
April 15	....	..	....	.....	.....	Salvarsan 0.30 gm.	
April 23	±	3	+	0.2 c.c. ++	.....	Salvarsan 0.30 gm.	30 c.c. of 40%
April 30	±	..	....	.....	.....	Salvarsan 0.30 gm.	
May 7	±	6	+	0.2 c.c. ++	.....	Salvarsan 0.30 gm.	30 c.c. of 40%
Sept. 23	±	19	+	0.3 c.c. ++	.....	Neosal. 0.90 gm.	
Oct. 8	±	..	....	.....	.....	Neosal. 0.90 gm.	
1913	Cholesterin-heart antigen.						
Jan 31	+±	70	+	0.2 c.c. ++	0.1 c.c. ++	Neosal-varsan 0.75 gm.	
Feb. 7	+±	57	±	0.2 c.c. ++	0.2 c.c. ++	Neosal-varsan 0.90 gm.	30 c.c. of 40%
Feb. 14	+±	28	±	0.3 c.c. ++	0.2 c.c. ++	Neosal-varsan 0.90 gm.	30 c.c. of 40%
Feb. 28	++	17	±	0.3 c.c. ++	0.2 c.c. ++	Neosal-varsan 0.90 gm.	30 c.c. of 40%
Mar. 14	+	14	−	0.2 c.c. ++	0.2 c.c. ++	Neosal-varsan 0.75 gm.	30 c.c. of 40%
March 27	++	7	+	0.5 c.c. ++	0.3 c.c. ++	Neosal-varsan 0.75 gm.	30 c.c. of 40%
April 9	+±	7	+	0.5 c.c. ±	0.3 c.c. ++	Neosal-varsan 0.90 gm.	30 c.c. of 40%

Case 152.—O. F., a man, aged thirty-two years, who illustrates both the result of intraspinous treatment and the necessity of continuing some form of treatment until the cerebrospinal fluid is normal. He had a well-marked tabes of three and one-half years' duration, with severe shooting pains. Previous to his admission he had received very little antisyphilitic medication. In the first year he received 2.2 grams salvarsan in eleven intravenous injections, which resulted in slight reduction in the degree of pleocytosis, a moderate reduction in globulin, and as far as could be determined, little if any effect on the Wassermann reaction in the cerebrospinal fluid. Then in one month's time he had 1.5 grams salvarsan in five intravenous injections plus three intraspinous injections, a total of 36 c.c. of his own serum. This resulted only in a reduction of the pleocytosis. For the next eight months he refused to have systematic treatment. In January, 1913, the pains became more severe, and about the end of the month he developed diplopia. Examination of the cerebrospinal fluid revealed a more marked pleocytosis than on any previous examination. In the next two months systematic treatment, consisting of seven intravenous injections, a total of 5.8 grams neosalvarsan, and six intraspinous injections of his own serum, a total of 72 c.c., resulted in a reduction in cells to nearly normal, and a marked decrease in the intensity of the Wassermann reaction in the cerebrospinal fluid. At the same time the pains and diplopia disappeared. The symptomatic relapse and the increase in the signs of the active pathological process as shown by the cerebrospinal fluid in this patient is in striking contrast to the subsequent course of the disease in those patients whose cerebrospinal fluid had been rendered normal by treatment.

Case 113.—W. L. S., a man, aged fifty-two years, who had a moderate tabes of seven years' duration. The principal symptom was shooting pain. In the first ten months of treatment he had seven intravenous injections of salvarsan, a total of 1.8 grams, and six months' mixed treatment. This resulted in a reduction in cells from 72 to 36 per c.mm., and a moderate decrease in globulin. In the next three months he received 2.5 grams salvarsan in nine intravenous injections and nine intraspinous injections of his own serum, a total of 109 c.c. At the end of this course of treatment the cerebrospinal fluid was normal except for a trace of globulin. Because of the persistence of a positive Wassermann reaction in the blood, intramuscular injections of mercury were given, but could not be tolerated long. Occasional lumbar puncture showed that the cells were increasing slightly in number, and systematic intravenous treatment with neosalvarsan was given. After five treatments, a total of 3.3 grams, it was found that the spinal fluid again showed a positive Wassermann reaction with 0.4 c.c. This returning reaction cannot be attributed to the increased sensitiveness of the cholesterin-heart antigen, because the reaction was negative in

January with the same antigen. This patient has shown less symptomatic improvement than any of our other patients. After a course of treatment there would be some decrease in pain and periods of a week or more without pain, but no permanent relief has been obtained. The return of the positive Wassermann reaction in the cerebrospinal fluid seems to indicate that the

TABLE X.—No. 113, W L. S., aged fifty-two years; tabes dorsalis, seven years; syphilis, twenty-three years; improvement; relapse.

	Blood.	Cerebrospinal Fluid.			Treatment.	
Date. 1912	Wassermann reaction.	Cells per cmm.	Noguchi globulin.	Wassermann reaction.	Intravenous.	Intraspinous serum.
March 7	++	72	++	0.1 c.c. −		
March 11	++	..	....	....	Salvarsan 0.35 gm.	
March 28	++	27	++	0.1 c.c. −	Salvarsan 0.50 gm.	
April 4 to	+	..	....	....	Mixed	
May 22 to	++	..	....	....	treatment	
Oct. 5	++	..	....	....	by mouth.	
Oct. 7 to	±	..	....	....	Salvarsan	
Nov. 4	±	..	....	....	5 x 0.20 gm.	
Nov. 5 1912	....	36	+	0.1 c.c. −		
Jan. 5	+	24	++	0.4 c.c. ++	Salvarsan 0.3 gm.	30 c.c. of 40%
Jan. 13	+	30	+	0.4 c.c. ++	Salvarsan 0.3 gm.	28 c.c. of 40%
Jan. 21	++	10	++	0.4 c.c. ++	Salvarsan 0.3 gm.	20 c.c. of 50%
Jan. 27	+	8	++	0.5 c.c. ++	Salvarsan 0.3 gm.	25 c.c. of 40%
Feb. 3	+	28	+	0.4 c.c. ++	Salvarsan 0.3 gm.	30 c.c. of 50%
Feb. 10	++	5	++	0.4 c.c. ++	Salvarsan 0.3 gm.	30 c.c. of 50%
March 16	+	9	+	0.5 c.c. +	Salvarsan 0.3 gm.	30 c.c. of 40%
March 23	+	3	+	0.4 c.c. ++	Salvarsan 0.2 gm.	30 c.c. of 40%
April 6	±	3	+	0.5 c.c. −	Salvarsan 0.2 gm.	30 c.c. of 40%
April 13	+	3	±	0.5 c.c. −	Salvarsan 0.3 gm.	
May 27 to	....	..	....	....	6 injections Hg salicylate	
July 8	....	..	....	....	intramuscularly.	
Sept. 13	+	2	±	0.5 c.c. −	Neosalvarsan 0.90 gm.	
Sept. 21	±	..	....	....	Neosalvarsan 0.90 gm.	
Nov. 23	....	6	+	0.5 c.c. −		
1913	Cholesterin-heart antigen.			Cholesterin-heart antigen.		
Jan. 25	++	9	±	0.5 c.c. −	Neosalvarsan 0.60 gm.	
Feb. 8	+±	..	....	....	Neosalvarsan 0.60 gm.	
Feb. 22	++	..	....	....	Neosalvarsan 0.60 gm.	
March 8	+±	..	....	....	Neosalvarsan 0.75 gm.	
March 22	....	..	....	....	Neosalvarsan 0.75 gm.	
April 5	++	7	+	0.4 c.c. +±	Neosalvarsan 0.60 gm	

syphilitic process is still active in some part of the cerebrospinal axis. The disappearance of the reaction under combined intraspinous and intravenous treatment, and its reappearance under intravenous treatment, alone seems to point to the advantage of the combined method in this patient at least.

The cases cited above are only examples of the various groups of patients whom we have under treatment. From the experience

of the past two years we now feel that 0.2 gram or 0.3 gram salvarsan is too small a dose, and that neosalvarsan given in the same relative amounts as salvarsan is much inferior to salvarsan. At present we are giving full doses of salvarsan—0.45 gram to 0.5 gram— every two weeks, and in addition intraspinous injections of 30 c.c. of 40 per cent. serum, until the cerebrospinal fluid shows a normal cell count and a negative Wassermann reaction. Under this plan of treatment many of the cases are showing more rapid improvement than did those treated a year or more ago, and illustrated in these tables. Unfortunately, our experience with general paralysis is too limited to give definite results. One patient with early paresis and one or two others who are borderline cases between tabes and paresis have shown a rapid decrease in pleocytosis and a moderate decrease in the globulin, but the Wassermann reaction has been slower in showing a response. When one considers the anatomical difficulties in reaching the myriads of spirochetes that are present in the brain in this condition, he is impressed with the necessity of prolonged and vigorous treatment.

Another point brought out by the work here presented is that the treatment of the chronic syphilitic diseases of the central nervous system is not the administration of two or four intravenous injections of salvarsan, or the exhibition of a certain amount of mercury and iodides. Each case presents a slightly different problem, and must be considered individually. Some respond much more rapidly than others, but the object in all should be to obtain a persistently normal cerebrospinal fluid. Of course we cannot state with certainty that a normal cerebrospinal fluid assures us that there will be no further progress of the degenerative process. All we can say is that as long as the cerebrospinal fluid gives evidence of a specific pathological process in the central nervous system, and we have specific therapeutic measures which will remove that evidence, these measures should be applied. Only when the fluid has become normal are we justified in discontinuing the treatment, and observations of the fluid should be continued so that at the first evidence of relapse, treatment may be resumed.

The method of intraspinous injection is not presented as a substitute for any of the accepted forms of treatment, but as an aid

in attacking these severe infections. We feel that there is definite evidence that this form of treatment has a curative action on the syphilitic process, and that therefore its combination with intensive intravenous treatment is indicated where specially intensive treatment is required as in rapidly advancing tabes or paresis, or where the disease has resisted other forms of treatment.

DISCUSSION

Dr. C. F. Hoover: What would Dr. Swift regard as a fair test of the efficacy of mercury in these cases?

The most obstinate visible lesion of syphilis is interstitial keratitis, and very vigorous treatment is necessary to affect it; the condition will not respond to small doses, but may require as much as two grains of the biniodide of mercury subcutaneously every day.

Perhaps the doses of mercury in the cases cited were not large enough.

Dr. S. J. Meltzer: The therapeutic idea here described by Dr. Swift is a very happy one; and this form of therapy cannot be compared to other forms of intraspinal medication.

The giving of antimeningitis serum is rather simple, because here we are engaged in purely local therapy; the organisms can be killed in the cerebrospinal canal just as well as *in vitro*.

But this is not the case in the treatment of syphilis. Salvarsan, according to Ehrlich's idea, must be split in the body before it can attack the organism of syphilis; therefore, Dr. Swift's idea was a happy one: To utilize the body to produce this splitting up of the salvarsan, and to attack the syphilitic lesions with serum containing this split product.

Dr. Swift: I would reply to Dr. Hoover that we do not feel that six injections of mercury should be regarded as a sufficient test of the efficacy of mercury; but in the case in which this was the extent of the mercurial therapy, it was impossible to continue the treatment. However, several of our cases had had the most vigorous mercurial treatment possible, and these cases have shown the most remarkable improvement of the cerebrospinal fluid after the use of the serum intraspinously.

In extending Dr. Meltzer's remarks, I would say that Ehrlich has demonstrated that salvarsan has some effect on spirochetes *in vitro* when they have been passed through the body; and our experiments have shown that salvarsanized serum will kill spirochetes *in vitro*.

CONCERNING THE ETIOLOGY OF HYPERTROPHIC PULMONARY OSTEOARTHROPATHY WITH A REPORT OF FIVE ADDITIONAL CASES

By HARLOW BROOKS, M.D.
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The general characteristics of this disease picture are now quite commonly known so that failure to recognize it can no longer be held accountable for the relatively few cases reported in the literature of medicine. Neither can the small number of instances recorded be solely accounted for from the excessive rarity of the condition for sporadic cases particularly of the minor types occur not uncommonly in almost every clinic. For example, in many cases of chronic empyema lesions of this character appear in mild, but unmistakable form to disappear when the pleural abscess is evacuated.

The infrequency with which the condition is reported must then be accounted for by the fact that clinicians take very little interest in the process, since it is universally believed to be secondary in nature and to represent but a relatively unimportant phase of a general condition.

Although I am myself also of this opinion, my interest has been kindled in the etiology of the syndrome, not only in an attempt to explain its origin, but also because I have wondered why it was not present in conditions in which it would be naturally expected to develop. This case analysis and study is designed to clear up these phases of the subject.

The chief interest must now centre in an explanation of why the characteristic deformities appear. From a cursory review of the literature of the subject the point of greatest perplexity would

seem to be the widely different conditions in which it appears, and the reason why it does not develop more frequently in apparently analogous circumstances, if, as Marie originally postulated, the picture is entirely secondary in nature.

The most constant and essential anatomical alteration appears to be an osteoperiostitis ossificans, effecting chiefly those parts of the long bones which are distally located, rather about than of the articulations. In young cases particularly, however, the bones entering directly into the articulations appear to be chiefly involved, apparently more because it is in these locations that hyperplastic processes, as it were, are more naturally or easily incited than from any inherent peculiarity of the articulations themselves. Hence it would seem that the condition is unfortunately termed an arthropathy, for it appears to be chiefly the peripheral nature of the bones rather than anything else which determines the process at these points.

As to the precise histological type of the bony changes, considerable natural variation exists as is also the case in most other forms of hyperplastic and retrogressive bony processes. As for the changes in the soft parts, little discrepancy exists when the anatomical facts are simmered down to their essentials and are divested of the natural variations which occur in practically all pathological manifestations. The clubbing of the digits is thus shown to be chiefly due to changes in the soft tissues, perhaps mostly in the areolar connective tissue. Whether fat production is the chiefest change as stated by Thoburn, or the connective-tissue elements of the true skin as asserted by Hirschfeld is relatively unimportant. Sternberg found round-cell infiltration and thickened bloodvessels in the pads which occur almost constantly in the thickened fingers. Is it not, however, to be expected that such alterations and variations should develop in digits in which the capillary circulation is always found to be so markedly slowed and changed? Although it is admitted that the enlargement of the ends of the fingers and toes is chiefly due to changes in the soft parts, *x*-ray and postmortem studies demonstrate that occasionally an osteophytic formation is found associated with the alterations in the areolar tissues.

The lack of association with other trophic alterations and the almost absolute dissociation of this syndrome from all neuropathic diseases indicates the absolute separation of this condition from the neuropathic arthropathies, and thus far microscopic studies of the diseased tissues also exclude lesions of this character.

The more recent histological studies of the disease, especially the carefull work of Franchini,[1] corroborate the constancy of the above outlined lesions. The studies of Ball and Alamartin[2] and Lienaux[3] on the lower animals, in apparently similar disease pictures, apparently completely identify the changes occurring in these animals as similar to those in man, at least in their essential substance.

It is then to the study of the etiological relationship of the primary disease changes to the characteristic deformities that I particularly desire to draw attention, and for this purpose I have attempted to carefully analyze the cases reported since 1903, at which time Janeway[4] brought the subject up to date in so far as case analysis is concerned.

I have chosen to limit my analysis to the instances thus recently reported, because it would seem from them, since there is no doubt both that pulmonary osteoarthropathy is itself better understood now, and particularly that acromegalia and the numerous arthropathies are now more certainly differentiated.

To this list I wish to add the case reports of five new instances of this condition which brings the total number of cases which I have personally studied and reported up to nine.

Notwithstanding the fact that the profession is now generally correctly informed in regard to pulmonary osteoarthropathy, one still finds in the literature a certain number of cases reported which cannot be considered as true pulmonary osteoarthropathy.

Such is the instance recorded by Mercy and Guillemot,[5] in which the description of lesions and symptoms seem to indicate that the case was one of rheumatic arthritis complicating rachitis. Case V

[1] Rev. crit. di. clin. Med. Scienze, 1910, xi, 745.
[2] Rev. de chir. Paris, 1908, xxxviii, 472; Gaz. d. hôp. of Paris, 1912, xxxvi, 1587.
[3] Bull. Acad. roy. de méd. de Belg. Brux., 1909, 4th e., xxiii, 108.
[4] Amer. Jour. Med. Sci., 1903, n. s., cxxvi, 563.
[5] Bull. et Mém. Soc. méd. de hôp. de Paris, 1903, ss., xx, 328.

of Symes, Thompson[1] is also in the doubtful class because of the fact that the description of the lesions taken together with the history of congenital syphilis suggest strongly the possibility of a luetic arthritis, by no means a rare condition. Although aside from the possibilities, since the etiological factor was lues, no pulmonary or cardiac explanation of the bony changes is given. None the less in recognition of the acknowledged familiarity and learning of the author in regard to this disease, the case can certainly not be excluded and must be considered in our analysis.

Symons[2] records also a doubtful case which relying sôlely on the author's description would apparently more completely fit into the picture of an arthritis deformans perhaps, or that of an incompletely developed acromegalia, but as with the instance just mentioned this one also cannot be definitely excluded. Somewhat similar to this case is that of Koll,[3] in which the marked changes noted in the lower jaw and in the tongue suggest acromegalia, particularly as no etiological factor is presented except the history of a long-standing intestinal toxemia while the history and course would further suggest the likelihood of an acromegalia.

Shaw and Cooper[4] describe under this heading a case which is definitely one of simple clubbed extremities due to heart disease of congenital origin—there is no ground whatever insofar as the meager report of this case goes why it should be included for a moment as one of pulmonary osteoarthropathy. Chrysospathes[5] records in a case in which multiple arthritis, partly of a suppurative character, was present. Although the urine showed a diminished excretion of phosphorus, the radiographic examination showed osteoporosis and thickening, and we cannot but agree with the author that the case was not one of pulmonary osteoarthropathy.

Because of the present inaccessibility of the journals in which the reports were printed, a list of eight articles is included in the appended bibliography, which could not be reviewed in time for the meeting of this Association.

[1] Medico-Chi. Trans., London, 1904, lxxxvii, 85.
[2] India Med. Gaz., 1904, xxxix, 16.
[3] Deutsch. Med. Woch., 1906, xxxii, 527.
[4] Trans. Clin. Soc., London, 1907, xi, 259.
[5] Zeitschr. f. Orthop. Chir., Stuttgart, 1908, xx, 406.

With these possible exceptions considered as among the questionable cases, all of the other instances reported are apparently true examples of this condition.

Of the total of 57 cases thus collected it is very significant that 44 instances showed definite pulmonary or pleural lesions, which were supposed to be of sole or chief etiological import. To this list should also be added the instance recorded by Thiraloix and Jacob,[1] which is undoubtedly a typical instance of the disease, and in which the history states that the patient was a chronic sufferer from asthma; at six years of age he had a fracture of the thorax, he had bronchial catarrh and emphysema, and yet the authors record the pulmonary condition as "normal," and further state that the etiological factor was not apparent. For obvious reasons I include this case with my list of those showing lesions of the pleuropulmonary tract, thus bringing the total list of cases of this type up to 45. It is also quite probable that Case V of my newly recorded cases is one of pulmonary origin, but inasmuch as the history is not clear on this point, and as we were unable to definitely locate either pulmonary or other primary lesions, this case is held in the doubtful list as regards etiology.

As to the precise character of the pulmonary lesions: 28 cases showed either pulmonary fibrosis, chronic bronchitis, or bronchiectasis; 6 cases showed neoplasm of the lungs; 1, atelectasis of long standing; 4, empyema and 6 pulmonary tuberculosis. It should be noted that in all these instances deficiencies in pulmonary parenchyma with presumable deficient pulmonary oxidation and extensive capillary compression were manifest.

Seven cases are recorded in which mediastinal neoplasm appeared as the most likely etiological factor. In every instance of this group, either clinical signs or autopsy findings showed invasion of the pulmonary tissue as well as that of the mediastinum. Two of these instances were cancer, with apparently secondary invasion of the mediastinum and lung. Two instances were sarcoma, one endothelioma, and two growths of unknown nature. One of these, Case III, of Symes, Thompson[2] had been previously reported as

[1] Bull. et mém. Soc. méd. de hôp. de Paris, 1910, 3d s., xxix, 51.
[2] Medico-Chi. Trans., London, 1904, lxxxvii, 85.

free from pulmonary lesions, but later study developed the finding here recorded.

Two cases remain in which no apparent etiological cause is present, the case of Wolfsohn,[1] in which lues was most likely the etiological factor, and Case V of my own newly recorded group.

The remaining five cases are those of Mercy and Guillemot discussed and excluded above in which the probable etiologic factors are stated to be rachitis and rheumatism; Case V of Symes, Thompson, and the very questionable case of Symons, and that of Koll, and one of my own. It would thus appear that of the total number of fifty-seven cases all except five showed invasion of the lung tissue, either primarily or secondarily. Of these five cases, two only are certainly examples of pulmonary osteoarthropathy, and the remaining three, while included in the group, are doubtful instances.

From this group it then appears that those of mediastinal neoplasm to all intents and purposes may be included with those in which the process appears primarily in the lung parenchyma or pleura. Inasmuch as the effects on the peripheral circulation and on the blood are substantially the same in mediastinal neoplasm with pulmonary involvement as in primary obliterative pulmonary disease, it would seem just that these two factors be considered as essentially identical.

Basing then our consideration of the etiology on the prevailing factors present in the recently reported cases, it would seem that the end results in practically all undisputed instances are peripheral venous stasis, due to mediastinal or pulmonary compression with limitation of pulmonary action and capillary circulation.

Circulatory lesions exclusive of mediastinal neoplasms were reported as present in but seven of the cases analyzed, and of these four instances were of such relatively unimportant (etiologic) alterations found at postmortem, as brown atrophy of the heart (two instances), fatty heart (two instances, one with a coronary sclerosis). In one case a clinical diagnosis of "possible myocarditis" was made and in but a single instance was the circulatory lesion,

[1] Berlin. klin. Woch., 1911, xlvii, 1031.

judged by the reporter to be etiologic. This was the certainly incorrectly diagnosticated case of Shaw and Cooper,[1] in which a congenital defect in the intraventricular septum was found. Inasmuch as this case differed in no respects from the usual case of clubbed extremities universally seen in congenital heart defects, it cannot be classed as one of hypertrophic pulmonary osteoarthropathy, and may therefore be safely discarded as before mentioned.

Since the anatomical characteristics of this symptom complex are essentially those of proliferation of the periosteum at the distal ends of the long bones, not truly an arthropathy, and proliferation of the soft tissues in the peripheral portions of the body associated with local congestive conditions, it becomes important in an attempt to explain the etiology of these lesions to consider the age at which these changes usually develop. In 43 instances the probable age of onset could be determined with a fair degree of accuracy. It was found that the average age of onset was at 17.55 years. A review of the statistics collected in Janeway's article, as in that of others who have also compiled the literature in regard to this condition, showed the notable fact that the neoplastic instances, as a rule, occur in those of a more mature age. In this series this same feature is also apparent, and it is found that the average age at onset in cases of probable neoplastic origin is 40.5 years. That a hyperplastic process should spring up in the tissues of the body in adult life in cases of new growth is of course quite in consonance with our present conception of the relationship of new growth formation to tissue hyperplasia.

The similar tendency toward general tissue hyperplasia in tuberculosis is also well established and need therefore cause no surprise when it occurs at any age. The average age of onset in cases due to tuberculous disease of the lungs is 29.6 years. When cases of neoplastic and tuberculous origin are excluded from our analysis, it is found that the average age of onset of pulmonary osteoarthropathy is but 12.67+ years, which would then place the disease as definitely of juvenile origin except in tuberculous and neoplastic instances. That in youth hyperplasia should be easily excited in

[1] Trans. Clin. Soc., London, 1907, xi, 259

the periosteum of the distal portions of the long bones and in the peripheral soft tissues of the body where chronic passive congestion of these parts is associated with deficient oxygenation and capillary stasis is then but a condition or result to be entirely expected.

It is a well-established fact in pathological anatomy that cyanosis, especially that due to pulmonary lesions or to mediastinal compression, causes the most marked stagnation in the periphery of the circulatory tree, namely, in the fingers, toes, and face. Recognizing the universality of clubbed fingers and toes in this symptomatic complex, it should then be expected that like changes should appear in the face, just as they so appear in most analogous conditions. It would therefore seem that the signs of globular nose tip and malar puffiness should be present in this disease. Such was the case in the four instances originally reported by me,[1] and in four of the new cases reported with this paper. Insofar as one may depend upon illustrations and text descriptions, these signs were present in several other instances recorded in this analysis. In Case III of Symes, Thompson group, the patient noticed that the nose was notably large at the tip. The questionable case of Symons shows also this feature, but this is probably not an instance of true pulmonary osteoarthropathy. The plates exhibited with the cases reported by Wynn[2] show an apparent, malar prominence and globular nose tip. The author, however, reports the face as normal and one must recall in the study of all photographs, especially those not skilfully posed, that there is a tendency toward the production of an apparent larger nose tip through foreshortening. The photograph of the case of Cagnetto[3] shows an apparent prognathism and prominent globular nose tip. The questionable case of Koll, already mentioned as probably one of acromegalia, shows this change quite typically. Krüger[4] mentions changes in the bones of the skull of a character probably similar to the changes to which I call attention. In the article of Ball and Alamartine,[5] they show from their studies of a similiar

[1] New York Med. Jour., December 16, 1911.
[2] Birmingham Med. Rev., 1904, lv, 139, 212.
[3] Rev. veneta. di. s. c. med. Venezia, 1906, xlv, 15.
[4] Virch. Archiv, 1906, clxxxv, 43.
[5] Rev. de Chir. de Paris, 1908, xxxviii, 472.

disease in the dog, that any part of the skeleton, including the bones of the face, may be involved. The case report of Mouisset and Orsat[1] presents a plate in which a large globular nose is apparently present. Wolfsohn[2] reports that the nose became broader and plumper and that the inferior maxilla became more prominent, features which the plate published with the paper shows in an apparently definite way.

Thus of the 57 cases included in this analysis, 15 probably show in greater or lesser degree this entirely to be expected facial alteration which has apparently escaped the observation of most students of the disease thus far. In reviewing, for my own satisfaction, the literature of this disorder published anterior to the period at which I chose to begin the present analysis, I find also not infrequent plates indicating this peculiarity.

Of direct bearing on the question of the etiology of pulmonary osteoarthropathy is the fact that those instances in which improvement followed treatment were all those in which pulmonary lesions were apparently the etiologic factor. When these lesions were of such a character as to permit of successful treatment or amelioration, improvement in the bone and soft tissue deformities are reported. Acting on this suggestion in a case of my own,[3] vigorous and persistent treatment designed to relieve the pulmonary lesions was continued over two years time. In addition to affording great relief from the conditions of fetid bronchitis and bronchiectasis, complete disappearance of the bone pains has followed, together with a considerable decrease in size of the fingers, toes, and of distal portions of the arm and leg bones. Similar results are recorded by Sevestre, Symes, Thompson, Wynn, Puyhaubert, Alexander, Robinovich and Barot, and Pic. Since all these instances were those of supposed pulmonary etiology, and since the improvement of the bony and soft tissue deformities appeared coincident with the betterment of the thoracic (pulmonary and pleural) disease, it would seem beyond doubt that a causal relationship existed between the primary and the secondary lesions.

[1] Lyon méd., 1911, cxvii, 337.
[2] Berlin. Klin. Woch., 1911, xlviii, 103.
[3] Case IV, New York Med. Jour., December 16, 1911.

It is unnecessary in this place to go fully into the discussion of all the various theories advanced to explain the almost invariable association of pulmonary, pleural, or mediastinal lesions in their relationship to the development of the characteristic osseous and soft tissue changes of pulmonary osteoarthropathy. The original theory of Marie must, however, be mentioned, since it was the first to be founded on a study of the pathological anatomy of the condition, and which also first recognized the dependence of these lesions on mediastinal, lung, or pleural changes. Marie believed that the deformities were due to absorption of some toxic substance from the lungs and pleura which were the seat of an inflammatory process. This theory received a certain amount of corroboration from those numerous instances of empyema and bronchiectasis in which the absorption of a septic poison was quite justly assumed to take place. That the absorption of septic material alone was insufficient to cause the deformities is clear from their absence in such conditions as hepatic abscess, chronic sepsis, osteomyelitis, and so on. This theory has, it is true, received the support of some reported cases, none such, however, appear in the recent literature since the differential recognition of the various arthritic processes has become sufficiently certain. This theory has been also discredited by frequent examples of pulmonary osteoarthropathy in cases such as pulmonary fibrosis or atelectasis where neither bronchitis nor bronchiectasis, or other septic absorption can be assumed to take place, and also by the frequent cases of mediastinal tumor which are also devoid of this possibility. It is obvious then that some other explanation must be advanced to explain this association of lesions because analysis of the most recently and probably most accurately observed cases indicate the practically invariable association of mediastinal, pulmonary, or pleural processes in the disease.

Apparently the true key to the dependence of this syndrome on mediastinal and pulmonary defects is furnished in Zeigler's discussion of the dependence of passive hyperemia on pulmonary defects. Briefly he states that in consequence of disease of the lungs and also of the pleura, in that it displaces the lung, the respiratory movements of the chest are hindered and thereby a withdrawal

of an efficient aid to the circulation occurs. In addition and of even more definite influence are those diseases which, as in pulmonary fibrosis or pulmonary compression from empyema, cause an impermeability of a more or less great area of the lung capillaries. Exactly similar conditions may be produced, as Zeigler pointed out in his memorable lectures on hyperemia, by aneurysm of the aorta or by tumors situated at or about the root of the lung, and which thereby compressed the pulmonary arteries.

An hyperemia so produced naturally is most marked or longest present in the peripheral portions of the body where, due to simple mechanical reasons, it becomes most manifest in the hands and wrists, the feet and ankles, and to a lesser degree in the face.

The effects of a long-standing passive hyperemia on bone or on areolar connective tissue is to induce hyperplasia of those parts of the bone or soft tissues which are most susceptible to hyperplasia, that is, the periosteum and the areolar connective tissue. Hyperplasia in these structures is the natural outgrowth of a passive hyperemia. This result is manifestly more likely to be carried on to a marked degree in young tissues, those which are physiologically most inclined to hyperplastic growth. Hence it is that the changes are the more pronounced in youth and less so or absent in adult or old age. This would apparently account for the almost strict limitation of pronounced cases of the deformities characteristic of pulmonary osteoarthropathy to those instances in which the process originated during youth. It also accounts for the failure of these changes to develop to such a degree or so frequently when the pulmonary obstruction occurs after youth. When the impediment to pulmonary circulation and respiratory movements is removed, as after treatment, the deformities should be checked or retrogress, as instances in the recent literature have shown them to do in pulmonary osteoarthropathy.

The reason why mediastinal growths produce precisely similar changes to those of direct pulmonary impairment is apparent and needs no further elaboration.

That defective oxygenation of the blood may play also a rôle in this tissue hyperplasia is possible, since it is well known that suboxygenated blood or a passive congestion invites abnormal tissue

hyperplasia, as witness, for example, the interstitial hyperplasia in chronic congestive diseases of the liver and spleen.

Septic absorption may perhaps play a similar role in some instances, but that it is in any way an essential in the evolution of these deformities would appear to be negatived by the evidence adduced from the analysis of these recently reported cases of pulmonary osteoarthropathy.

In conclusion then it would seem that a quite sufficient explanation of the lesions of pulmonary osteoarthropathy and their dependence on pulmonary functional limitation or on such mediastinal growths as impede pulmonary circulation is furnished by the resultant passive hyperemia which these conditions produce in the distal portions of the body.

The lesions are most marked and most likely to appear in those instances where the process begins in early youth because all tissue hyperplasia is most easily excited during this period. They appear in lesser degree or not at all when, as in most cases of pulmonary tuberculosis, the pulmonary and circulatory impediment develop at a period of life when hyperplasia of the periosteum and areolar connective tissue is less readily excited.

Case I.—Montefiore Home. J. P., male, aged nineteen years, born in Russia; single; occupation, tailor.

Family History. Mother and father alive and in good health. One brother and one sister alive and well. Two sisters and one brother died in childhood. No history of tuberculosis, syphilis, or of chronic metabolic or nervous affections in family. No consanguinity.

Previous History. Patient is the fifth child, healthy from infancy up to about the age of ten years.

Habits: Appetite always good, bowels regular, used to sleep well. Drank tea and coffee moderately. Moderate in the use of beer and whisky. Never smoked or chewed. Denies all sexual relations, venereal diseases, or masturbation. Worked as a tailor in dust-laden air and under very poor hygienic surroundings. Says that in the shop where he was employed a tuberculous patient was working.

Previous Diseases. As a child he had measles and whooping cough. At the age of nine years he had pneumonia on left side. At the age of twelve years and again at fourteen years he had other attacks on the same side.

Present History. Dates back about five years. At that time while recovering from pneumonia he began to cough and expectorate moderately. These symptoms became aggravated at times and continued until about two years ago, when he began also to feel quite weak. About three years ago he suffered from a burning sensation in the back; he also noted slight bulging of back in the left side. This gradually increased so that a deformity resulted which made him walk about in a stoop-shouldered manner. He has a left-sided inguinal hernia of about four years' standing which appeared as a result of the constant coughing. About a year and a half ago he noted that his sputum was blood-streaked. This persisted for about one week, then ceased, but again reappeared in June, 1912.

FIG. 1.—Pulmonary osteoarthropathy. Case I.

The sputum is very copious. It is greenish-yellow in color, is fetid, and has a sweetish, nauseating taste. At the present time he chiefly complains of burning pain in back and legs, so severe that he cannot walk. He feels very weak generally. During his coughing attacks he feels dizzy and has a sensation of seeing stars. He has occasional night sweats. He sleeps well at night, but is obliged to get up to urinate about twice every night. He passes large quantities of urine each time. During the day he urinates about every half hour. On two occasions the abdomen became distended

considerably for three-day intervals. For the last three months becomes very dyspneic on slight exertion. He is very tired and weak and complains of palpitation.

One month ago edema appeared in both lower extremities below the level of knee-joints, this disappeared in two weeks after external application. There are no symptoms relating to the alimentary tract.

Chief Complaints. (1) Bulging of entire left chest; (2) marked cough and copious, fetid, sweetish tasting, occasionally blood-streaked sputum; (3) polyuria; (4) dyspnea and palpitation on slight exertion; (5) asthma.

Physical Examination. General Appearance: Young adult male of medium stature and poorly nourished. The musculature is flabby. Skin, cool, dry, and pallid. The expression is that of anxiety and suffering. Head, normal shape, no scars, depressions, or elevations except that malar bones are very prominent and the end of nose is globular. The eyes show normal pupils. No ocular palsies or nystagmus.

There is very marked clubbing of fingers and toes, and the distal extremities of long bones of ankles and legs are enlarged and tender. *X*-ray examination show clubbed fingers and toes to be chiefly due to hyperplasia of the connective tissue, but the distal extremities of the long bones show very marked proliferative periostitis.

There is marked bulging of entire left chest, seemingly this half of thorax is displaced to the left and there is marked scoliosis in the dorsal region, the convexity directed to the left.

Lungs: The vocal fremitus is markedly diminished over left chest anteriorly from about level of fourth rib and posteriorly from level of spine of scapula. Hyperresonant percussion over entire right lung. Over left lung, hyperresonant anteriorly on the left side above level of fourth rib and from the level of the fourth rib in upper half of left axilla a tympanitic note is given. Posteriorly on the left side there is a tympanitic note about the level of the spine of scapula, below and up to about the fifth dorsal vertebræ. Diminished resonance to flatness from fifth dorsal vertebræ down to base. The respiratory murmur is exaggerated over the entire right lung. Expiration is about equal in the duration to inspiration. The respiratory murmur is diminished all over the left lung and markedly so below the level of the fourth rib anteriorly, in the axilla (left) and posteriorly from level of fifth. No rales were heard.

Heart: The apex-beat is located in fifth space, nipple line. The cardiac dulness above begins at lower border of fourth rib and extends on the left three-fourths inches beyond nipple line and on the right to the midsternal line only. First sound is of fair muscular quality, best heard in fifth space in nipple line. There are no murmurs or abnormal sounds present. The peripheral arteries show signs of thickening. The radials are equal, show moderate tension, are compressible, regular, rate 100 per minute.

Abdomen: Panniculus adiposis scant. Soft, flat, no areas of tenderness or rigidity. No palpable masses.

Liver dulness begins in fifth space and its flatness extends about two inches below costal margin. The inferior border is smooth and firm. The spleen and kidneys are not palpable.

The neurological examination gives negative findings.

Urine Examination. Color, amber, clear; reaction, acid; albumin, 10 per cent. (volume); specific gravity, 1015; urea, 10 grams; sugar, none; indican, no excess; bile absent; acetone and diacetic acid absent. Many finely and coarsely granular, hyaline, and epithelial casts.

Sputum. Purulent, contains very much pus, occasional epithelial cells. No elastic fibrils. Blood cells present. Bacteria very abundant, mostly pyogenic organisms. No tubercle bacilli found; chemical tests show much albumin present.

Chief Complaints. Frequent cough with very copious sputum. Dyspnea and exhaustion. Pain and tenderness in wrists and ankles.

Diagnosis. Chronic bronchitis with bronchiectasis, pulmonary fibrosis, and chronic adhesive pleurisy, chronic parenchymatous nephritis, and possibly spinal caries and hypertrophic pulmonary osteoarthropathy.

Course. The patient was confined to bed because shortly after entering the hospital he developed marked edema, ascites, and defective fluid excretion. Under hot packs, reduced fluid intake, saline purgation, and salt-free diet, these symptoms became much relieved and coincidently the sputum became much reduced in quantity. The odor diminished and the patient's general status much improved. Especially notable was a decrease of the tenderness and pain in the wrists and ankles, and an apparent decrease in the clubbing of fingers and toes.

He is still confined to bed and will probably so remain for considerable time yet. Physical and *x*-ray examination of the chest show no apparent morphological changes, but the general picture has much improved.

Case II.—Montefiore Home, application No. 14,125. Mrs. T. W., female, aged thirty years; occupation, cook; born in Russia; in United States eight years.

Family History. Father died at the age of eighty years. Mother is alive and healthy. One cousin on father's side died from consumption. No rheumatic, malignant, or syphilitic history.

Personal History. First child, naturally born and breast fed. Had smallpox at the age of eight years. Malaria at the age of ten years. First menstruated at the age of seventeen years, regular twenty-eight day type, five days' duration. Married at the age of eighteen years, husband twenty-eight years. She had two children, both of whom died in infancy from intestinal disturbances.

Habits. Tea in moderation, no alcohol. Lived under good sanitary conditions.

Present Illness. Was comparatively healthy until five years ago, when she was taken sick with pneumonia, had chill, pain in chest, hemoptysis, and high fever. Was very ill for six or seven days, when conditions improved somewhat, but the cough persisted and expectoration became very abundant, associated with slight daily rise in temperature. About two months before entering the hospital the patient had a severe pulmonary hemorrhage which left her in a very weakened condition. After this the

FIG. 2.—Pulmonary osteoarthropathy. Case II.

cough became less severe and she improved slowly but was obliged to remain in bed for one year and a half after this attack. The cough has since become continuous and the expectoration is very abundant and often blood tinged. She has lost a great deal of strength and flesh. Vomits frequently. Has occasional diarrhea. She has night sweats and continued pain in the chest.

Physical Examination (on admission). Female, nutrition fair, not very emaciated or anemic. Panniculus adiposis moderate. Weight, 120 pounds.

Skin, dark and dry. Pupils equal and react to light and accommodation. No apparent oral or nasal disturbance. The face as a whole is cyanotic, and the malar prominences and the nose are noticeable, the latter being of a definitely globular form. Teeth in fair condition, but many of the upper ones are missing. Tongue clear and moist, fine fibrillary twitching. Pharynx clear, not congested. Neck shows a few palpable lymph nodes, and some are also found in the axilla.

Thorax symmetrical, no depressions or protrusions. The respiratory movements are labored, sixty per minute.

Heart: Apex-beat not seen or felt. The right border lies at the mid-sternal line. The left border three inches to the left of the median line. No murmurs or other abnormal sounds are heard.

Lungs: Chest expansion equal on both sides, but is slight and the accessory muscles are called into play. Tactile fremitus is very feeble on both sides. The right apex is hyperresonant on percussion and the left apex even more markedly so. Numerous mucous, sibilant, and sonorous rales are heard all over the lungs. The breath sounds are exaggerated and expiration is prolonged.

The fingers and toes are markedly clubbed and very cyanotic. The distal extremities of the radius, ulna, and of the tibia and fibula are enlarged, tender, and painful. The extremities are cold, their capillary circulation is stagnated but there is no edema.

The neurological examination was negative except that a diagnosis of a complicating hysteria was made.

During the nine years which the patient has remained in the hospital numerous examinations of the urine was made. These were almost always negative except that when she had complicating surgical conditions albumin was occasionally present.

The sputum was almost continually very abundant and of a markedly purulent character. Tubercle bacilli have never been discovered and the predominating organisms appear to be members of the pyogenic group.

Examination of the blood and feces and of the gastric and duodenal secretions gave fluctuating conditions apparently independent of the disease for which the case is now reported.

Frequent *x*-ray examinations demonstrated a confirmation of the diagnosis of pulmonary fibrosis, emphysema, bronchiectasis, chronic bronchitis, and hypertrophic pulmonary osteoarthropathy.

Soon after entering the hospital the patient developed typical attacks of bronchial asthma; temporarily relieved by the usual treatment but becoming progressively frequent.

In March, 1910 the patient was successfully operated on for an acute appendicitis and at the same time a ventrosuspension of the uterus was done. Recovery was uneventful.

She had been treated variously, among the more unusual methods may

be mentioned exposure of the chest to the *x*-ray, deep intramuscular injections of crotaline, by radium emanations, injections of adrenaline, etc. Only temporary relief was attained by any of the methods employed.

In January, 1912, she was successfully operated on for gall-stones. Rapid convalescence took place in spite of the persistent cough, expectoration, and asthmatic seizures. Meanwhile the signs of pulmonary osteoarthropathy have slowly progressed and the pulmonary signs and symptoms have increased.

In April, 1912, the patient was operated on by Dr. Goodman in an attempt to relieve the emphysema. The details of this operation are herewith indicated.

April 16, 1912, operation. Incision parallel to right border of sternum. Exposed second, third, and fourth costal cartilages. The anterior layer of the pericondrium was reflected outward as far as the costochondral junction. The posterior perichondrium was then separated, and about one and one-fourth inches of the intervening cartilage removed. The resections were made with a scalpel, with the exception of the fourth, where the bone-cutting forceps were used in removing a small portion of the rib with the cartilage. The anterior layer of the pericardium was separated from the parietal pleura, and then reflected over the sternal end of the resected cartilage, where it was fastened with two or three fine chromic sutures. The overlapping ends of perichondrium were excised.

After bleeding was controlled, the pectoral muscles were united by chromic and plain gut, interrupted sutures; the skin with silk and cat-gut. No drainage. The same procedure was repeated on left side. Second and third costal cartilages excised. The cartilages on left side were found considerably enlarged and thickened. Simple dressing applied, and a bandage.

As each cartilage was removed the underlying pleura was seen to become markedly retracted with each expiration. The patient seemed to breathe easier and take the anesthetic more smoothly. The cyanotic appearance of the mucous membrane changed to a more pink color.

Since this last operation great improvement in the breathing and in the severity of the asthmatic attacks has taken place. The respiratory movements are more free but the patient still presents a typical picture of this syndrome. Under hospital discipline the hysterical manifestations have greatly decreased.

Case III.—M. B., female, aged nine years, history No. 2215 Montefiore Home.

Family History. Father, aged forty-two years; mother, aged forty-three years, three brothers and one sister all alive and well. Parents are first cousins. No tuberculosis or other familial disease present.

Personal History. The patient is the sixth child. Birth normal.

One hour after birth of child, mother noticed that she breathed with

difficulty, that respirations were apparently dyspneic and noisy. The attending physician stated at this time that the child had some congenital pulmonary affection.

She was breast fed but did not nurse readily and always coughed and often vomited after nursing. She slept badly and breathing continued to be peculiar. She had pneumonia three times, the first at one and one-half years, the second one month later and a third attack two weeks later. After these pulmonary attacks the mother noticed that the child was frequently blue and that her cough and breathing were worse. Aside from these attacks the child had no disease during early infancy.

FIG. 3.—Pulmonary osteoarthropathy. Case III.

She walked at twenty months of age and began to talk at about the same time. The first tooth appeared at the close of her first year, subsequent history of dentition is unsatisfactory. As far back as mother can remember the child has had frequent sweats, especially at night.

Up to last winter the child has apparently been getting worse insofar as the respirations are concerned, dyspena and cough are now continously present and she expectorates very freely after her coughing paroxysms. She complains of pain in the sides of the thorax, and last winter began to have "spells," which consisted of severe dyspena, cough, and cyanosis, especially of the face. She now has these attacks about twice monthly.

The child is always worse during the winter season. She lost several pounds in weight last winter, but gained while in the country during the past summer.

The mother noticed that the child's fingers and toes began to take on their present peculiar shape first about five years ago. Last winter from no apparent cause to the mother the finger tips became much swollen and the thumbs began to ooze blood along the bases of the nails—this hemorrhage continued off and on for weeks at a time.

Chief Complaints. Dyspnea, cough, and expectoration, pain in the left side.

Physical Status. The patient is a well-nourished but under-sized female child. There are no gross skeletal deformities and the panniculus adiposus and the skeletal musculature are well developed. The skin is warm, soft, and moist, well nourished. No eruptions or scars are present. The mucous membranes are deeply colored from a severe cyanosis.

The head is rather large and broad with a tendency toward the cubical type and with marked protrusion of the forehead, and malar prominences. There is a flattening of the nasal bridge and the tip of the nose is cyanotic and bulbous in shape. The face is full and "bloated," especially the cheeks and lips, which are quite cyanotic, while the whole cast of the countenance, with the narrowed eye slits, is suggestive of the Mongolian type, or as expressed by a member of the house staff, like that of a "miniature squaw."

Dyspnea is apparent even at rest from the movements of the alæ nasi and from the thoracic movements and posture. These become exaggerated on exercise. The vision is good and the ocular movements normal. The pupils are equal and normal in their reactions. The conjunctivæ are of good color.

The tongue is rather large, flabby, and somewhat cyanosed. The teeth are in fair condition, a few are missing and the insertion mucous membrane is ulcerated in a few instances. The mucous membrane of the hard and soft palate and of the pharynx is moderately cyanotic.

The vessels of the neck show moderate pulsations. No lymph nodes in the neck are palpable. The thyroid is not readily palpable and the neck is short and stubby. No thymus dulness or shadow can be made out.

The thorax is definitely of the rachitic and pigeon-breast type, and the left side is more prominent than the right, which is smaller, depressed anteriorally. There is a marked left shoulder drop, some dorsal scoliosis, and the scapulæ are prominent. There are no clavicular depressions.

The respirations are labored and stertorous. There is visible retraction in the clavicular and suprasternal fossæ. There is an audible respiratory grunt and the expansion on both sides is markedly deficient. On percussion there is a general boardy quality throughout with a small area of dulness at the right base posteriorly. Auscultation shows grunting respiration

with scattered rhonchi, sibilant, sonorous, and crepitant rales throughout. These latter are especially numerous over the left base, front, and back. Inspiration is short and expiration prolonged, averaging 50 per minute.

The area of cardiac dulness is distinctly enlarged. The apex-beat is visible and feebly palpable in the fifth interspace, $2\frac{1}{2}$ inches from the midline. The right border lies $1\frac{1}{4}$ inches beyond the midsternal line, the left border being just outside to the nipple line. The heart action is regular, rapid, the sounds at the apex and at the aortic areas are natural, and neither murmurs nor thrill can be made out even after exercise, which seems to be well borne insofar as the heart action is concerned.

The left pulse is apparently stronger than the right, the rate is 120 per minute and no other abnormalities are apparent.

The abdomen is rigid. There is no pain or tenderness, no palpable masses, or abnormal pulsations. The liver dulness is one finger's breadth below the costal margin, but because of the abdominal rigidity the edge cannot be palpated. The spleen and kidneys are not palpable. There is marked clubbing of the finger and toe tips with considerable cyanosis, some pain on severe palpation but none in the wrists or ankles, which are enlarged and roughened insofar as can be determined from palpation. The finger and toe nails are much thickened and sharply curved. There is no edema although the appearance of the tissues would on inspection suggest this, insofar as the extremities are concerned.

The neurological status was reported as normal by the attending neurologist (Dr. Abrahamson).

The child was found to be mentally bright, easily taught, friendly, and affectionate.

No reaction followed the injection of 0.5 mg. of old tuberculin.

Fluoroscopic examination (Dr. Gotleib) showed the right ventricle to be greatly displaced to the right, so that the shadow had the appearance of a transposed heart, extending over to the periphery of the thorax on the right, apparently inducing more or less rotation of the heart from the left to the right. There were numerous areas of pulmonary turbidity, apparently peribronchial in location but very irregulaly distributed. The hands and wrists show epiphyseal separation of the radius and ulna (both sides), marked thickening of the distal extremities of these bones and hypertrophy of the terminations of all the phalanges.

Frequent examinations of the urine gave negative results.

Examination of the blood showed: Hemoglobin, 90 per cent.; red blood-corpuscles, 4,960,000 per c.mm.; white blood corpuscles, 12,600; polymorphonucler neutrophiles, 58 per cent.; small lymphocytes, 15 per cent.; large lymphocytes, 22 per cent.; large mononuclears, 1 per cent.; basophiles, 1 per cent.; eosinophiles, 3 per cent.; no normoblasts, macro- or microcytes.

Examination of the very abundant sputum showed it to be muco-

purulent in type, to contain many epithelial cells, occasional red-blood cells, many pigmented pus cells and leukocytes, plugs of pus and mucous. No elastic fibrils. Bacteria very numerous, chiefly comprising pus organisms. No tubercle bacilli found and no demonstrable pneumococci.

Diagnosis. Chronic bronchitis and bronchopneumonia with probably pulmonary fibrosis. Displaced and dilated heart (well compensated). Hypertrophic pulmonary osteoarthropathy.

The child remained three months in the hospital and is still under occasional observation. During this period she made considerable progress insofar as relief of the pulmonary conditions are concerned but without apparent improvement of the bone lesions. She progressed rapidly under the instruction of the hospital school, and close observation of her case convinced us that the original assumption of a cretinoid condition was incorrect.

Case IV.—Mr. T. A. E., seen in consultation with Dr. E. D.

Male, aged fifty-one years, from an ancestry distinguished for both physical and mental vigor. Family history negative as to all systemic or hereditary taints.

Previous History. As a child he was frail. He contracted and suffered severely from nearly all the usual infections of childhood. Only constant and highly skilful supervision succeeded in bringing the child to maturity. He was particularly prone to catarrhal affections of the bronchi and upper respiratory tract and was long thought to be tuberculous, though at no time were tubercle bacilli detected in the sputum.

At the age of twenty-nine years the patient suffered from a severe attack of bilateral lobar pneumonia, from which he made a slow recovery, after which, tuberculosis being suspected, he was sent West, where he embarked upon a ranching venture in Wyoming. The patient greatly improved under these conditions of life, though subject to privations and exposures to which he had never been accustomed. He ceased to have fever, cough subsided, and he soon found himself able to do a "man's work" as a cowboy. The life was extremely congenial to him, and this may in part account for some of the benefit derived from it.

During 1898 he served throughout the Spanish-American war in a volunteer cavalry troop, and though the service was almost constantly in the tropics he was able to stand the work well, and was returned to his home station in fairly good condition.

Social and business obligations recalled him to New York, where he again began to suffer from frequent attacks of bronchitis, manifested by fever, persistent productive cough, and loss of strength and weight.

The patient has at times indulged unwisely in both alcohol and tobacco. He now drinks practically nothing except on rare social occasions, but still smokes excessively. He has never suffered from any venereal infection, and has lived a moderate sexual life.

Present History. October 23, 1912. The patient came to me after contracting a recent "cold" which had manifested itself by increased cough with profuse purulent expectoration and pain in the chest, particularly over the right upper lobe. The appetite was poor, he was constipated and weak, and slight alterations in temperature causes him to sneeze and to experience chilly sensations. Temperature 98.4°, pulse 78, respiration 20.

Physical Examination. The patient is a tall, large framed man. The extremities are large and powerfully muscled, but the hands and feet are proportionally large and cumbersome, and they show marked clubbing of the digits with thickening of the nails and moderate cyanosis.

The face is somewhat congested, the skin thick and turbid, the malar bones are very prominent, tender on deep pressure, and the end of the nose is typically globular. Frontal alopecia is marked and rapidly progressing.

The thorax is long, barrel-shaped, considerably flattened above, immobile. Aside from moderate carination the abdomen is negative.

The ankles and wrists are markedly enlarged and thickened; roughness and tenderness of the periosteum are apparent on firm palpation.

The heart is displaced to the left, but is apparently not enlarged. The muscle tone is poor but no murmurs can be elicited, even after exercise which gives rise to considerable dyspnea. The retrosternal dulness at the base is not increased. There is no tracheal tug or other evidence of aneurysm, aortitis, or mediastinal growth.

Examination of the lungs shows areas of diminished resonance associated with increased vocal and tactile fremitus at the apices on both sides and over the entire base on the right. The breath sounds are greatly and irregularly altered over these areas, varying from frank bronchial breathing to the subdued and distant type. Numerous, sonorous, and bubbling rales are present, changing from time to time as the patient coughs.

The sputum is purulent, abundant, and has a peculiar sweetish, though not fetid odor. It contains numerous pus and epithelial cells, various cocci and bacilli, a few diplococci, but no tubercle bacilli.

Examination of the nervous system and of the genito-urinary tract gave entirely negative findings.

The von Pirquet tuberculin reaction was found negative. At times the patient complained bitterly of pains in the ankles, wrists, and in the shafts of the long bones as well.

The diagnosis was pulmonary fibrosis with chronic bronchitis, probably originating from an incomplete resolved pneumonia, and causing the development of hypertrophic pulmonary osteoarthropathy.

As the patient failed to respond to the usual methods of treatment for chronic bronchitis he was advised to go South for the winter. I am told that the bronchitis has now subsided and that the acute symptoms of cold are much relieved, though the dyspnea remains the same.

Case V.—Patient, M. B., laborer, aged twenty-four years, born in Russia, entered the second medical service of the City Hospital in March, 1913. The history had to be obtained through an interpreter as the patient spoke only an unusual Russian dialect. He entered the hospital with the chief complaints of pain in the epigastrium and in the back.

Fig. 4.—Pulmonary osteoarthropathy. Case V.

Family History. The patient has been a laborer; he has used alcohol and tobacco moderately. During his childhood he suffered from the usual diseases of childhood, including smallpox. He has also suffered from not infrequent attacks of bronchitis, and at one time was quite seriously ill from such an attack, from which, however, he states that he quickly completely recovered.

Venereal infection is denied. He has suffered from no intercurrent diseases except from occasional attacks of cold and cough, but on none of these occasions has he been seriously ill. He lost 15 pounds in weight during the past year. He had no cough, no night sweats, the feet have,

however, been occasionally swollen and painful, the wrists have also at times been painful though never acutely so. These bone symptoms have lasted on occasions for the past ten years. The patient states that his father, one brother, and his son, now three years of age, have all had large hands and feet similar to those which the patient himself has.

He now complains chiefly of sharp pain in the epigastrium and of occasional pain in the back. He is unable to give an actual description of these pains, but from what can be obtained from him through an interpreter it would seem that these pains are probably myalgic in character.

Status. The patient is a well, nourished and well developed male of about twenty-four years of age. He does not appear to be acutely or seriously ill.

Head. The hair is abundant and normal. The eyes are normal, the pupils equal, regular, and react to light and accommodation. The ears and nose are negative. The teeth and mouth are in good condition. The tongue is clean and normal. There is no globular enlargement of the nose or thickening over the malar processes, as is so frequently seen in cases of this disorder.

Thorax. The apex-beat is seen and heard in the fifth interspace, $3\frac{1}{2}$ inches to the left of the midsternal line. The heart rate is 68 per minute. The rhythm is regular and no abnormal sounds are present, except that after vigorous exercise a soft systolic murmur appears both at the mitral and at the aortic areas. No dyspnea is elicited upon exercise. The respiratory movements are somewhat restricted, although the thorax is well and symmetrically developed. There is an area of dulness extending downward from the level of the third dorsal spine posteriorly on the right side, finally merging below with liver dulness. The respiratory sounds over this area are somewhat restricted in transmission, but there is no apparent change in fremitus. Many small mucous rales are found over the entire thorax, particularly over the bases, but otherwise no definite lesions can be made out in the chest. Frequent examinations of the chest fail to show constant signs except for the flattened percussion note already indicated. Rales are constantly present but differ very much in distribution, character, and frequency.

The veins over the thorax and abdomen and those of the upper extremities in particular are somewhat congested. The feet and especially the finger and toe tips are very much cyanosed. The cyanosis is increased on exercise.

The abdomen is negative except for the presence of a few fibromas or lipomas embedded in the subcutaneous connective tissue of the abdominal wall. The hepatic border lies at the costal margin. The spleen and kidneys are not palpable, due to the rigidity of the abdominal muscles.

The Extremities. The hands and feet are very large. The wrists and ankles are thick, large, and the periosteum is apparently thickened over the distal end of each of the long bones. The fingers and toes are very

much clubbed. The nails are thickened, dark blue in color, and very much curved. The subcutaneous tissue of the hands and feet is apparently hypertrophied but the bones do not appear to be insofar as can be determined by physical examination.

The ankles are particularly enlarged and the skin over them and the feet is chronically cyanosed almost edematous, but tips only slightly on pressure. He complains that when he is on his feet for a long time considerable pain appears in the ankles, and when he is standing it seems that a slight degree of pes planus is present.

Examination of the Blood. Hemoglobin, 83 per cent.; red blood cells, 5,700,000; white blood cells, 10,000; differential leukocyte count, polynuclear cells, 54 per cent.; lymphocytes, 43 per cent.; mononuclears and transitionals, 3 per cent. Examination of the urine is entirely negative.

Radiographic examination of the hands and feet (Dr. Hirsch) shows an enlargement of the soft tissue of these members, but there is no increase in the bony structures of either hands or feet, except that exostoses of the terminal phalanges are present to some extent. The periosteum covering the distal extremities of the long bones of the leg and of the forearm shows a marked zone of proliferation.

The Wassermann reaction was found negative. The patient had no fever, while in the hospital and in a short time was entirely free from pain and willing to leave for home.

He was given no treatment of any definite character, it being simply designed to keep him in the hospital for observation. Frequent examination of the chest failed to elicit any definite condition, although rales could be found at almost any time. Nevertheless considerable cyanosis was constantly present in the extremities, and on exercise it also appeared over the thorax and abdomen but with very slight tingling of the face and entirely without dyspnea.

Because of the characteristic changes in the extremities the case was diagnosed as one of pulmonary osteoarthropathy, but unlike the instance previously observed no primary pulmonary or mediastinal lesions could be definitely made out although they were suspected. The patient gained weight constantly while in the hospital, ate his food well, and appeared to be perfectly happy and contented.

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THE DIAGNOSIS OF PULMONARY ABSCESS

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The present study was suggested by the very striking number of pyogenic complications (empyema and abscess of lungs) which were associated with the pneumonia cases in the medical service of the Pennsylvania Hospital during the past winter. This article is based essentially on a review of all the cases of pulmonary abscess recorded in the *autopsy reports* of the said hospital and covers a period of fourteen years, 63 cases in all. Two cases of abscess following the inhalation of foreign bodies are added to the series. The frequency and seriousness of local pyogenic complications following pneumonia is still insufficiently realized and many text-books devote but little space to their consideration. The article does not concern itself with examinations by means of the bronchoscope, the *x*-ray, or the blood. Our statistics, of course, present the darkest side of the picture as they deal exclusively with fatal cases.

Our figures show a striking contrast both as regards etiology, symptomatology, and physical signs when the cases of single and multiple abscesses are contrasted.

Single Abscesses. Total 30 Cases.

Sex.
- Male . . 24
- Female . . 6

Diagnosis.
- Correct . . 10
- Missed . . 16

Subdiaphragmatic
- Correct . 2
- Missed . . 2

Location.
- Right upper lobe . 7
- Right lower lobe . 11
- Left upper lobe . 1
- Left lower lobe . 7
- Subdiaphragmatic right side . . 4

Left upper lobe
- Loculated: No communication established . . . 2
- Associated with empyema . 5

Size. Marble to 12 x 11 x 9 cm.; 9 x 5 cm.; 8 cm.; 10 cm.

This table emphasizes the frequency with which single abscesses are situated in the right lower lobe. The reason is presumably

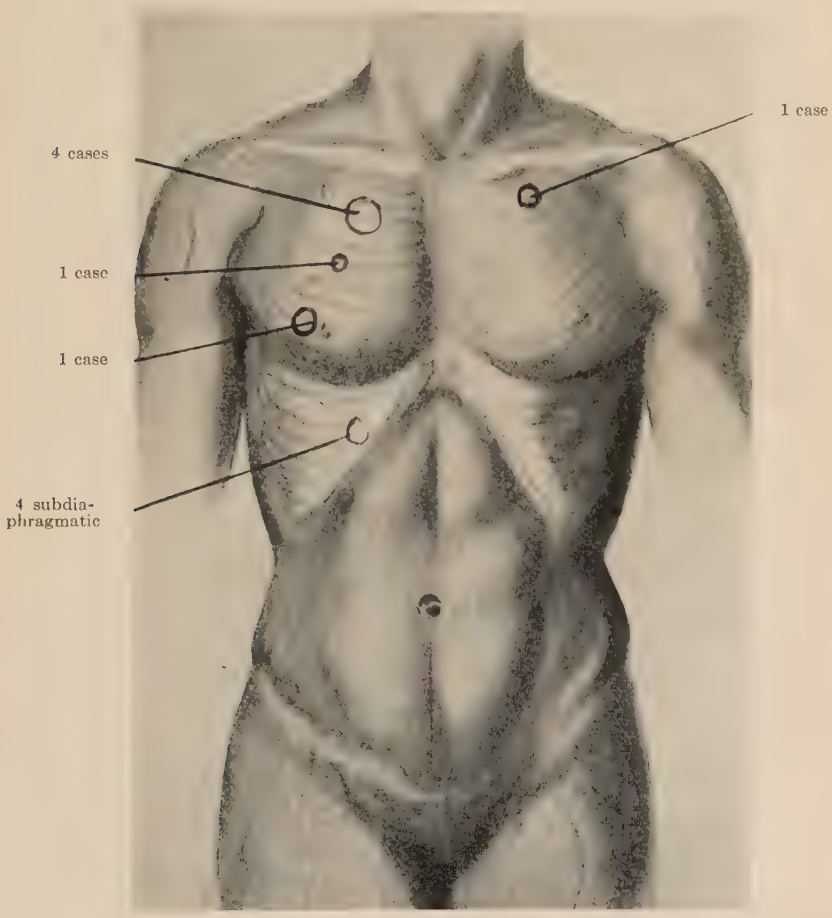

FIG. 1.—Diagram illustrating the relative frequency and position of pulmonary abscesses. The circles in Figs. 1 and 2 show the location of the single abscesses. The different diameters represent the relative size of the abscesses.

that pneumonias and especially interlobar empyemas are more common on the right side (Figs. 1 and 2).

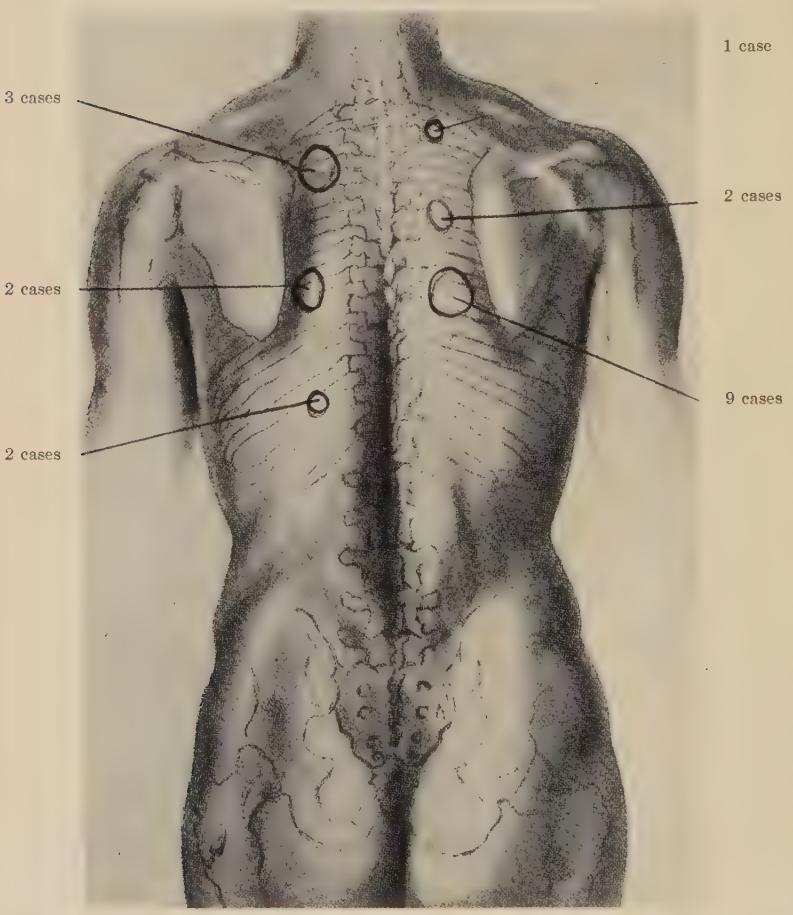

FIG. 2.—Diagram illustrating the relative frequency and position of pulmonary abscesses.

ETIOLOGY

Suppuration in abdomen	4
Rupture of cancer of esophagus into lung	1
Thrombosis of branch of pulmonary artery: typhoid	1
Croupous pneumonia	9
Endocarditis (vegetative)	4
Bronchopneumonia	2
General septicemia	1
Not determined	8

Foreign bodies: 1 tooth, 1 tack.

It is evident from the foregoing table that local lesions in the chest play the predominant etiologic role. We wish to emphasize the fact that although the statement is often made that an empyema ruptures into the lung and is evacuated through a bronchus, the opposite is what actually happens. The abscess or an interlobar empyema ruptures into the pleural cavity and causes an empyema, the pleura being much less resistant than the bronchus. In seven cases there was no communication between the abscess and the bronchus even at time of death.

The importance of foreign bodies as an etiologic factor of pulmonary abscess is, as the result of *x*-ray examinations, bronchoscopy, and of increasingly frequent operative intervention, becoming constantly more evident. Thus in one of our cases a tooth in another a brass tack caused the abscess. Külbs[1] reports 7 such cases among 24 abscesses and Guisez[2] has recently recorded 5.

SYMPTOMATOLOGY

Cough with paroxysmal expectoration (4 foul, 3 bloody)	10
Indefinite or absent symptoms	20

The occurrence of paroxysmal expectoration in large amounts, especially if malodorous and if it contains elastic tissue and no tubercle bacilli, leads to a correct diagnosis in many instances.

Symptoms were either not characteristic or entirely lacking in two-thirds of the cases.

THE PHYSICAL SIGNS. In 8 cases signs of cavity were present, in the remainder nothing definite was recorded. In 3 cases the physical signs were masked by pleural exudates. This occurred in 6 postpneumonic cases.

MULTIPLE ABSCESSES. Total, 33 Cases.

Sex	Male 29	Diagnosis	Correct 6
	Female 4		Missed 27

[1] "Ueber Lungenabszesse und Bronchiektasen," Mitteilungen aus den Grenzgebieten der Medizin u. Chir., 1912, Heft 3, 549.

[2] Bull. de la Soc. de Pediatrie de Paris, 1912, xiv, 56.

Etiology

Mastoid and thrombosis of lateral sinus and internal jugular	1
Otitis media	2
Otitis media and thrombosis of lateral sinus and internal jugular	2
Thrombosis of portal vein and mesenteric veins and appendicitis	2
Thrombosis of iliac vein	1
Bronchopneumonia	6
Croupous pneumonia	3
Typhoid and bronchopneumonia	2
Vegetative endocarditis	6
Abscess of kidney	1
of lip	1
of pharynx	1
of seminal vesicles	1
of skin	1
Gunshot wound of chest	1
Not determined	2
Total	33

The accompanying table shows the etiologic factors of multiple abscess to be quite different from those of the single lesion. In the former, suppurative foci of the most diverse kinds at distant parts of the body play the greatest part. This applies especially to involvement of the middle ear and to mastoid disease.

Symptomatology

Cough + bloody sputum	4
Cough + purulent sputum	1
Bronchopneumonia	4
No record	5
No record pulmonary symptoms	17

Physical Signs

Scattered rales	2
Scattered rales and friction rub	4
Scattered rales and areas of dulness	5
Areas of dulness, bilateral	4
Dulness, one base alone	6
Signs of cavity	1
No record	11

In one case a pyopneumothorax developed. In one case the cavities were situated at the periphery of the lung, the visceral layer of the pleura forming part of the walls. One case was diagnosticated because of profuse blood-streaked sputum, negative for tubercle bacilli. One case was recognized because of profuse

purulent expectoration and cavity signs. At operation pus was found, the patient died.

This study being based on autopsy statistics no conclusions can be drawn as regards operative mortality. We have made no allusion to the value of *x*-ray examinations as most of our cases died before the days of such diagnostic means. Great assistance both as regards the diagnosis and the topography of the lesion can often be drawn from such examinations, but the *x*-ray is by no means infallible in diagnosticating between consolidation and abscess. Since then a positive diagnosis is often impossible by any of the present methods, we feel that early surgical exploration is justified when the protracted course of the disease renders the existence of abscess probable, even when the exact focus has not been definitely localized.

So far as prognosis is concerned, this depends essentially in cases of single abscess on how early surgical intervention is employed. In the cases of multiple abscess the outcome is for obvious reasons practically always fatal.

DISCUSSION

Dr. M. H. Fussell: *X*-ray examination for lung abscess may give equivocal information. Last year I had a case of pulmonary abscess in which the *x*-ray plate left me in a quandary as to whether I was dealing with a consolidation or a collection of fluid; and a second case came to my notice just before leaving home in which the same doubt arose.

Dr. E. Libman: I have studied a number of cases of pulmonary abscess and have reached a few conclusions which I believe to be of value.

Lung abscess after pneumonia is not often a true abscess; the condition is due to the necrosis of the pneumonia with later breaking down of the tissues.

There is great diagnostic value in a necrotic odor to be detected in the breath; rather early in the course of lung abscess, this sign can be elicited by having the patient give a hard cough.

Another important sign is the appearance of an effusion over the abscess. When with a high temperature and the signs of effusion, an exploratory tap finds sterile fluid, one may conclude almost certainly that there is an underlying abscess.

Dr. George Dock: An *x*-ray plate should always be made when lung abscess is suspected; a solitary abscess may thus be shown very well. We have had several cases in which definite localization was accomplished by skiagraphy.

Bearing out Dr. Libman's statement, I recall one case in which there was distinct fetid odor to the breath before pus appeared in the sputum.

Dr. F. T. Lord: I think there are three symptoms which are most important:

1. A shadow in *x*-ray plates.
2. Elastic fibers in the sputum.
3. Circumscribed dulness.

Dr. P. K. Brown: In a number of cases of lung abscess I have noted the fetid breath as a prominent symptom.

Failure to locate the abscess in one case was explained later by taking stereographic plates. I think the use of stereoskiagraphy in all cases is desirable.

Dr. Norris: I merely wish to add that when the signs of pulmonary abscess are strongly suggestive, surgical intervention should be invoked before an irremediable destruction of lung tissue takes place.

THE CLINICAL FEATURES OF CASES OF SUBACUTE BACTERIAL ENDOCARDITIS THAT HAVE SPONTANEOUSLY BECOME BACTERIA-FREE

By E. LIBMAN, M.D.
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At the meeting of the Association of American Physicians in 1912, the writer[1] presented a paper on the results of a study of the endocardial lesions found in cases of subacute bacterial endocarditis (chronic malignant endocarditis, chronic infectious endocarditis, chronic ulcerative endocarditis, endocarditis lenta). After describing these lesions he presented evidence that the bacteria in such cases could spontaneously disappear from the lesions and that the lesions could heal in part or entirely. It was shown that the healing of the lesions was not necessarily accompanied by recovery from the clinical standpoint. There are two reasons for this. In the first place the healing of the lesions leaves fibrous and calcareous tags or masses which interfere with the usually already improper functioning of the valves and the musculature of the heart, and which may give rise to embolic phenomena. In the second place so much injury may be done to the kidneys and the blood-forming organs that although the bacteria disappear the damaged tissues cannot functionate to the extent necessary for the preservation of life.

In the paper referred to there were briefly presented notes on eleven cases, concerning which there was no doubt that the patients had suffered from subacute bacterial endocarditis and had spontaneously become bacteria-free. In three of these cases (these

[1] Libman, Amer. Jour. Med. Sci., September, 1912, cxliv, 313; Trans. Assoc. Amer. Phys., 1912, xxvii.

were the earliest cases) the condition was not suspected clinically, and the diagnosis was established by the evidence accumulated by a study of the postmortem material. In the other cases the diagnosis was made from the clinical features and proved by bacteriological and pathological investigations. The presence of the embolic glomerular lesions in the kidneys, described by Loehlein, and later by Aschoff, Baehr,[1] and Gaskell, we found to be pathognomonic of the existence of subacute bacterial endocarditis when due to the cocci usually found in such cases. In those cases which were due to the influenza bacillus, such lesions were not found. As such cases are quite infrequent, this is no evidence that such lesions cannot be produced by subacute or chronic endocarditis due to this organism.

It is my present purpose to give a short review of the clinical features of the bacteria-free cases that we have observed up to the present time. As it would not be possible, except in monographic form, to discuss these cases in detail, only certain important points will be mentioned. There will be appended a short description of the clinical course of each of the cases which were utilized in the course of the study.

In the earlier paper the following description was given of the clinical course of the cases seen up to that time:

1. They may develop a nephritis and die of uremia.

2. They present the picture corresponding to what we have been wont to call chronic endocarditis with fever (that is, they have a valvular lesion, more or less fever from time to time, usually low, occasional petechiæ, occasional joint symptoms, and embolisms). Some of these cases resemble cases in which bacteria are demonstrable in the blood. Some are pale, others more or less pigmented.

3. Some of the cases present a complex that appears to have been entirely overlooked. The striking feature is a peculiar diffuse brown (sometimes quite dark) color of the face. The rest of the body may show some pigmentation. There is evidence of a valvular lesion, there is more or less anemia, usually a palpable spleen, and usually also tenderness of the sternum. The patients feel

[1] Amer. Jour. Med. Sci., September, 1912, cxliv, 327.

weak and do not sleep well. Petechiæ occasionally occur. There is some fever from time to time, usually low. Erythrocytes are found in the urine in some of the cases. The subsequent history of such cases is not yet known; one case died with symptoms of cerebral embolism. The important feature of these cases is the curious change in the color of the face. Since I have observed it in bacteria-free cases, I have looked for it in cases in the bacterial stage, and, to my surprise, I find that while the faces of most of the cases are sallow, or of a rather white color, some develop a certain amount of brown or café-au-lait color.

4. They may go on with more or less anemia, and suffer from that and from decompensation.

In discussing the splenic enlargement which occurs in the bacteria-free as well as in the bacterial stage, I suggested that from observations made several years before, I had reason to believe that a case would occasionally be found in the bacteria-free stage in which marked enlargement of the spleen might be a very conspicuous feature of the case. I suggested that when such a case did come under observation, it might be regarded as a case of Banti's disease plus chronic valvular disease, and that it might not be recognized that the case was really one of subacute bacterial endocarditis in the bacteria-free stage, with marked enlargement of the spleen as the most conspicuous feature. During the last year I saw a case which showed that such a clinical picture is possible. A description of it is appended (Case XXI).

I have given the classification which I described in the paper published last year, because it is the basis of my present classification. After describing the mode of onset, the symptoms, and the termination of the cases in the bacteria-free stage, I shall show in what way I have found it necessary to modify the classification.

The remarks which follow are based on a study of 21 cases of subacute bacterial endocarditis in the bacteria-free stage; 4 of the patients are still alive. Postmortem examinations were made in 16 of the 17 cases that succumbed, and in all there was ample proof from the clinical, bacteriological, and pathological studies that we were dealing with the disease under discussion. In the course of the investigations, 1 case was encountered which was suspected

of being in the group, but there was not sufficient evidence present at the postmortem examination to corroborate the clinical suspicion. This case is mentioned among the appended notes, but is not described in detail. It will be of service on another occasion when the question of differential diagnosis is taken up. Up to May, 1910, the writer had observed 43 cases of subacute bacterial endocarditis.[1] Since that time he has made more or less comprehensive studies of 82 more cases, the entire number being 125. Of the 82 cases seen since May, 1910, 18, or over one-fifth, were in the bacteria-free stage (1 case became bacteria-free under observation, Case VIII). The writer is convinced that a careful study of all the cases of chronic valvular disease seen at the hospital during that period would have resulted in unearthing a larger number of cases. It is only by a careful scrutiny of all cases supposed to be instances of uncomplicated chronic valvular disease that one becomes impressed with the frequency with which patients are found suffering from chronic valvular disease plus the bacteria-free stage of subacute bacterial endocarditis.

We will now proceed to a review of some of the clinical features of the disease:

Duration. This is difficult to estimate, as most of the cases were not seen in the bacterial stage, and therefore one can have no idea of the length of the bacteria-free periods. In Case VIII, in which influenza bacilli were found for almost two months, the later bacteria-free period was about four months. There is sufficient evidence to show that the bacteria-free period may last for two and a half years, as in Case XIII. In two cases there was a history of the presence of cutaneous tender nodules three (Case XX) and three and a half years (Case XIII) before death. It is to be remembered that there are a few records in the literature of cases in which patients became bacteria-free under observation and remained well except for the presence of the previously existing valvular lesion. But the period of observation in these cases was not very long when the cases were reported, and no later reports have been issued which state whether the patients developed any

[1] Cf. Libman, Amer. Jour. Med. Sci., October, 1910.

of the special features to which we have drawn attention as occurring in the bacteria-free stage.

Previous History. In one case there was a history of scarlet fever at an early age. In a number of cases there was a history of previous attacks of rheumatism and of the establishment of a valvular lesion. In some cases the patients had suffered for a longer or shorter time from palpitation, dyspnea, pain in the precordial region, and cough with or without expectoration; at times the sputum was hemorrhagic.

In a few of the cases there was a history of an attack of fever, pains in the joints, palpitation, and dyspnea a number of months before the development of the symptoms for which the patient came under observation. It is proper to suspect that these attacks in some instances represent the bacterial stage of the disease. A critical analysis of the data bearing on this point will be submitted at another time.

Mode of Onset. In most of the cases the early symptoms were cardiac in nature. There were dyspnea, palpitation, and cough with or without hemorrhagic expectoration. With these symptoms there might or might not be chilly sensations, fever, sweats, joint pains, and swelling of the legs. In one case severe pain in the thigh was the first symptom (due to an embolic aneurysm of the femoral artery). In another, a severe pain in the sacral region was the prominent early symptom (this is at times observed also in the bacterial stage of the disease). Vomiting associated with headache and dizziness was the initial symptom-complex in a couple of cases; in one case epistaxis, and in another, purpura first appeared. Frequency of urination was a striking symptom that appeared early in two cases.

Fever. The temperature in the bacteria-free cases does not run as high as in the bacterial cases. It may be high in cases that are seen, apparently, shortly after the bacterial stage has ended, or if complications develop or an intercurrent disease. Embolisms may cause marked rises of temperature, and at times chills, even though there be no bacteria in the pieces thrown off from the valves. In some cases the temperature is practically normal during almost the entire period of observation.

Valvular Lesions. In every one of the cases there was evidence of an organic lesion of the mitral or aortic valve, often of both. As a rule no new murmurs developed during the disease.

Renal Phenomena. This subject is very important in connection with the symptomatology of the bacteria-free stage of subacute bacterial endocarditis, but it is possible now to give only the shortest account of our observations. Macroscopically hemorrhagic urine usually occurs either when the case comes under observation shortly after the bacterial stage is ended (as made apparent by the clinical pictures or by the study of the age of the vegetations found in the heart) or as the result of gross embolic lesions of the kidney. Erythrocytes in small numbers are found in the urine in a number of the cases, but not with the regularity or persistence with which they are found in the bacterial stage of the disease.

Albumin and casts are found in some of the cases from time to time. In others there is definite evidence of a more or less marked progressive disease of the kidney. In this latter group of cases there are two types. In the one there is passed a subnormal, normal, or increased quantity of urine of a normal or subnormal specific gravity, albumin and formed elements being more or less conspicuously present. In the cases of the second type there is passed a large amount of urine (up to 2700 c.c.), with a high specific gravity (up to 1028 or 1032), and this may occur even when there are present but a few formed elements and only a trace of albumin. This second clinical type of renal disturbances has not, as far as the writer knows, been previously described. The relationship of the clinical phenomena and the pathological lesions is worthy of a special study.

Symptoms due to renal insufficiency were prominent in a number of cases; in some they dominated the clinical picture. In one case (Case III) the examination of the fundus revealed edema of the optic disks and retina. As will be seen later, renal insufficiency was the main cause of death in a comparatively large number of cases.

Blood Changes. In the cases in which examinations were made (and they were made in nearly all) there was found a more or less marked anemia, always of the secondary type. The hemo-

globin in some cases was as high as 65 per cent., and in others as low as 35 or even 20 per cent. There was a tendency to progressiveness in the anemia in many of the cases. Nucleated erythrocytes were never found. The bone-marrow of the femur was examined in three cases, and was found to be dark red in color, and to show typical regenerative changes. In a fourth case the tibia was examined and fatty marrow found.

When the anemia was profound it was plainly revealed by the color of the skin and mucous membranes, and by a general edema most marked in the lower limbs.

The leukocytes were usually not increased in number except when complications ensued. In some cases the number diminished during the course of the disease (to 4000 at times). The polymorphonuclear cells were either normal or moderately increased (barring periods during which there were complications). In a few cases they diminished during the progress of the disease (in one case to 36 per cent.).

Splenic Enlargement. The spleen was palpable in all the cases except four. At times it was enormously enlarged. In all the cases but one of those in which the spleen was not palpable it was found enlarged at the postmortem examination, at times very much so. In a large percentage of the cases the Malpighian bodies in the spleen were conspicuously enlarged and, microscopically, hyperplastic.

Petechiæ. These were found at one time or other in 13 cases. They were located in the mucous membranes (especially the conjunctivæ) and the skin. As a rule few were found as compared with the number seen in cases in the bacterial stage.

Purpura. This was noted in three cases. In one it was the main symptom for two months before the patient came under observation. In another case it occurred repeatedly throughout the course of the disease.

Tender Cutaneous Nodules. These were found in only three cases. In two they persisted close up to the time of the fatal termination. One of these two patients had had these lesions for three years, and one for three and a half years.

Sternal Tenderness. This symptom, as the writer stated last year,[1] seems to be more marked in the bacteria-free stage than in the bacterial stage. It was found in all of the cases in which it was looked for. In one case the tenderness of the lower sternum was so marked that it was elicited by the lightest tap. The long bones were usually not found to be tender.

Sweats and Loss of Weight. These symptoms were not nearly as marked as in cases in the bacterial stage. In only a few cases is there a note of profuse perspiration. That loss of weight should not be a prominent symptom is evident from the fact that many of the cases have comparatively little fever as compared with cases in the bacterial stage.

Pigmentation. The brown color of the face was noted as a striking symptom in nine cases. In some of these it increased under observation. A few of the anemic patients whose faces were at first white, later developed a more or less marked café-au-lait tint. This has also been observed by the writer, as stated in a previous publication, in the bacterial stage, but the development of a marked brown color he has seen only in cases in the bacteria-free period.

Pains. The only pains that occurred with any frequency were joint pains. These occurred particularly in the cases in which purpura was a symptom. Reference has already been made to the case in which pain in the sacrum was a marked feature. Pains due to various complications need no discussion here.

Aneurysms. Apart from the occurrence of aneurysms of the mitral valve, the septum membranaceum, and the sinuses of Valsalva, which produced no recognizable symptoms, there was encountered once an embolic aneurysm of the femoral artery. The aneurysm had ruptured into the soft parts and had eroded the bone. The patient was sent into the surgical service of the hospital with a diagnosis of osteomyelitis, because of the rapidly developing large tender swelling, the fairly high temperature, and the high leukocyte count with polynucleosis. Because of the presence of a valvular lesion, a large spleen, and a marked anemia, I suspected that we were dealing with a case of subacute bacterial endocarditis.

[1] Trans. Assoc. Amer. Phys., 1912.

Further observation proved that this view was correct. The post-mortem examination corroborated the clinical opinion; the lesions were practically bacteria-free, and for the main part organized. This was in keeping with the fact that the three blood cultures made in the case gave a negative result.

Cardiac Symptoms. These can be classed in two groups. We must consider first the subjective and objective symptoms due to the valvular lesion as such. Here we include the palpitation, pains in the chest, dyspnea, cough, and expectoration, congestion of the viscera, edema of the legs, and hemorrhagic infarction of the lungs.[1] All these symptoms may occur in any case of valvular disease.

In the second group we include the embolisms, petechiæ, purpura,[2] embolic aneurysms, and tender cutaneous nodules; this second group of symptoms occurs when there are friable masses on the valves of the heart or on the wall. They are therefore common events in cases of subacute bacterial endocarditis in the bacterial or bacteria-free stage, and may well be called endocarditic symptoms. Cerebral embolism seems to be as frequent an occurrence in bacteria-free as in bacterial cases.

Joint Symptoms. These are much less common than they are in the bacterial stage. There may be joint pains or joint swellings, or both. Occasionally, as stated above, purpura is also present. The joint swellings are, as a rule, not marked, and are quite transitory. The writer does not remember having seen a joint that was markedly tender or over which the skin was red.

Cause of Death. The cause of death can be fairly definitely stated in 16 of the fatal cases: In 3 it was due to cerebral embolism, in 4 to uremia, in 2 to the progressive anemia and an intercurrent pneumonia, in 1 to uremia, embolism, and pneumonia, in 1 to pneumonia, in 3 to cardiac insufficiency, in 2 to progressive anemia, with concomitant cardiac weakness. To put the matter in another way, it may be said that cerebral embolism was a determining factor in 4 cases, uremia in 5 cases, intercurrent pneumonia in 4 cases,

[1] These are due oftener than is generally supposed to thromboses in veins of the lower extremities or of the pelvis.

[2] This could, of course, at times be due to a hemorrhagic diathesis.

anemia in 4 cases, and cardiac insufficiency (unaccompanied by profund anemia) in 3 cases.

The important role played by the progressive anemia, the nephritic changes, the presence of vegetations on the valves, and the improper functioning of the valves and musculature of the heart is thus made very clear.

The lesions found in the heart in all the cases were, in the main, of the same type as those described in the writer's earlier paper on this subject. In two cases atypical lesions were found, the main feature of which was a peculiar worm-eaten appearance of the mitral valve, which in both instances was the seat of an old mitral stenosis (Cases XIII and XX). In one of these two cases the glomerular lesions were of a diffuse type and the typical embolic lesions were not present. The clinical history was, however, quite typical, and the characteristic, tender, cutaneous nodules were seen by the writer.

General Grouping of the Cases. From the description which we have just given of the symptomatology of the disease under consideration it might appear that most of the cases look quite alike clinically. But while it is true that petechiæ, sternal tenderness, a palpable spleen, and a more or less marked anemia occur in most instances, the cases can be grouped according to certain features that particularly impress the observer. In the earlier part of this paper the writer quoted the classification of the cases that he attempted to make and which he presented last year, and he also drew attention to the occasional occurrence of an unusual enlargement of the spleen. The study of the additional cases seen since then, in conjunction with a review of the earlier cases, leads him to describe five prominent features, one or more of which may be found in a certain case and characterize the case, rather than describing four or five groups; for he has found there are cases that belong to more than one of the groups which he described last year.

The five prominent features which may be found are:

1. Marked progressive anemia.
2. Brown pigmentation of the face.
3. Marked evidence of renal disease.

4. Marked enlargement of the spleen. The spleen may be so enlarged that the case may be considered a case of chronic valvular disease associated with Banti's disease.

5. Phenomena due to the vegetations present on the valve. These are what I term endocarditic symptoms. They consist of more or less elevation of temperature occurring from time to time, petechiæ, occasional joint symptoms, and embolisms.

Whenever any of these clinical features are found in a case of chronic valvular disease it is of the greatest importance, for it draws attention to the possibility that the case is one of chronic valvular disease plus subacute bacterial endocarditis in the bacterial or bacteria-free stage.

Afebrile or nearly afebrile periods of fair duration (several weeks) or negative results of blood-cultures would help make the differentiation between the two stages.[1] The diagnosis from certain cases of acute rheumatic infection of a valve previously the site of disease, and from some other conditions may present difficulties. The writer will not discuss this question, as it is his purpose at the present time to describe clinical features and not differential diagnosis. All he wishes to state now is that studies made by Dr. D. J. Kaliski and Dr. P. Aschner have not demonstrated the value of complement fixation tests as an aid in the diagnosis of bacteria-free cases.

In the appended description of our cases, summaries are given which show which of the five important features of the bacteria-free cases occurred in each. A few examples will, however, be of interest here:

Case 1. Pigmentation; endocarditic symptoms.

Case 3. Nephritic symptoms.

Case 5. Endocarditic symptoms; progressive anemia.

Case 6. Endocarditic symptoms; intense anemia; pigmentation.

[1] It is an interesting fact that in cases of subacute bacterial endocarditis in the bacterial stage, bacteria can practically always be found in the blood if the temperature is not elevated a great deal. It is in the cases with high temperature and with very marked oscillations that one fails at times to obtain bacteria in the blood cultures, although the bacteria are present in enormous numbers in the vegetations in the heart.

Case 15. Pigmentation.

Case 21. Marked splenic enlargement; progressive anemia; renal symptoms.

Description of Clinical Course of Cases. In the following notes there will be presented a concise description of all the cases of subacute bacterial endocarditis in the bacteria-free stage that the writer has observed. As the cardiac lesions were described rather fully in the paper presented before the Association last year, and as it is his purpose at another time to publish these lesions in greater detail, he will, in the descriptions of the cases, refer to the postmortem findings in as brief a manner as possible. The renal lesions will also not be described at the present time, as they will form the basis of another communication. It is sufficient to state that in nearly all the cases the embolic glomerular lesions, which are characteristic of the disease (except when due to the influenza bacillus), were present. In a few cases these embolic lesions were associated with other diffuse glomerular lesions. In a few cases only diffuse lesions of the glomeruli were present. These lesions will be described at another time. In the few cases in which embolic lesions were not present, there was sufficient evidence present clinically (tender cutaneous nodules) or at the postmortem examination to put the cases into the group which the writer has termed subacute bacterial endocarditis in the bacteria-free stage.

A perusal of the following notes will show that the writer has included four patients who are still alive, all of whom are in quite good condition. Although the absolute evidence of the fact that they belong in this group is not forthcoming, the cases are so typical clinically and correspond so closely to other cases in which the clinical diagnosis was proved correct by postmortem examination that it seemed desirable to include them.

Case I.—Observed from July 2, 1905, to August 6, 1905. Three blood-cultures were made, with negative results. There was a previous history of scarlet fever at the age of two years; pains and redness of the joints during the last winter. Onset one month before admission, with cough and expectoration, cardiac palpitation, dyspnea, pain in both knees,

which were red and not swollen. The heart showed evidences of an aortic lesion. The face was markedly pigmented. The spleen was palpable and petechiæ were present. An embolic aneurysm of the iliac artery developed. The patient passed large amounts of urine, up to 2000 c.c. a day, containing a moderate number of leukocytes and hyaline casts. The leukocyte count varied from 6200 to 9200; hemoglobin, 65 per cent., later 61 per cent. The temperature rose at the highest to 101° or 102°, except just before the embolism occurred, due to which the aneurysm developed; at that time the temperature was 104°. The cause of death was apparently a cerebral embolism. Postmortem examination revealed a healed calcareous bacteria-free lesion[1] of the aortic valve, with an aneurysm of the mitral valve and fibrous lesions of the chordæ tendineæ. The spleen was large and showed marked hyperplasia of the Malpighian corpuscles and one infarction. In the kidney there was an embolic aneurysm.

Summary. The main features in this case were pigmentation and endocarditic phenomena (development of non-bacterial embolic aneurysms).

Case II.—Observed from May 1, 1907, to October 3, 1907. There were two blood-cultures, with negative results. There had been cardiac palpitation and dyspnea for six months. For two months prior to admission, attacks of purpura, and for five weeks edema of the legs were present. The cardiac lesion was apparently aortic insufficiency. The spleen was palpable just below the free border of the ribs and petechiæ were present. Perspiration was a marked feature. The urine varied in amount from 750 to 850 c.c. Specific gravity ranged from 1008 to 1012; erythrocytes were present, also hyaline and hyalogranular casts. Blood examination at first showed 5200 leukocytes, 53 per cent. hemoglobin, and 3,040,000 erythrocytes. Later the leukocyte counts varied from 4000 to 7000; the polymorphonuclear count was as low as 41 per cent., except a short time before death, when it was 68 per cent. The hemoglobin dropped to 38 per cent. The temperature was usually around 100°, occasionally 101°, except when an embolism occurred or when a purpuric rash developed. Death was due to cerebral embolism. The autopsy showed a calcareous lesion of the aortic valve and an aneurysm of the membranous septum. The spleen was almost twice the normal size, contained old and recent infarctions, and the Malpighian bodies were prominent. Areas of softening were found in the brain.

[1] This means that the cultures from the centre of the vegetations showed no bacteria, and that smears made from the crushed vegetations also showed no organisms.

Summary. The important features of this case were endocarditic phenomena (embolisms and purpura), marked enlargement of the spleen, urinary phenomena, progressive anemia, and lymphocytosis.

Case III.– Observed from November 9, 1905, to May, 1906, and again from October 3, 1909, to November 3, 1909. There was one blood-culture, with negative result. A history was obtained of rheumatism occurring two years before the date of the first admission. During the first stay in the hospital there were joint symptoms and a pericarditis. Hemoglobin was 86 to 90 per cent., but progressively dropped to 65 per cent. The temperature was at first up to 103°, afterward practically around normal, except with occasional rises to 101° or 101.2°. The quantities of urine varied from 620 to 1600 c.c. The specific gravity varied between 1008 and 1028, being usually around 1010 to 1020; there was present a faint trace of albumin, and occasional hyaline and hyalogranular casts. The spleen was not palpable. There were evidences of mitral insufficiency. On admission the second time the patient gave a history of having developed edema of the legs five weeks before. Ophthalmoscopic examination showed marked edema of the optic disks and surrounding retina. Hemoglobin dropped to 36 per cent. Urine quantity varied at first from 1300 up to 3000 c.c., and later dropped to 330 c.c. At the time of the second admission the urine contained a trace of albumin, numerous hyaline and granular casts, and leukocytes; later it was reddish brown in color, contained a heavy trace of albumin and numerous erythrocytes. The patient died of uremia. At autopsy there was found a fibrous lesion of the wall of the left auricle and fibrous and calcareous lesions of the chordæ tendineæ. The spleen was one and a half times the normal size.

Summary. The main features of this case were progressive anemia and renal phenomena.

Case IV.—Observed from April 24, 1910, to May 9, 1910. There was one blood-culture, with negative result. The patient had been dyspneic for one year. For two weeks there was vomiting, headache, and dizziness. There was evidence of mitral and aortic insufficiency; the spleen was palpable. There were no petechiæ. The patient looked anemic. Hemoglobin was 60 per cent.; leukocytes, 13,000; polymorphonuclears, 65 per cent. The urine varied in specific gravity from 1010 to 1013; there was present a faint trace of albumin, occasional hyaline casts, erythrocytes, and granular casts. The temperature was never over 102°, usually between 99° and 100°. The patient died of uremia, cerebral embolism, and a terminal

pneumonia. The autopsy showed old pericardial adhesions and a lesion of the wall of the left auricle and of the chordæ tendineæ, which was almost entirely healed. The spleen was one and a half times the normal size, and contained infarctions.

Summary. Renal phenomena, old pericarditis, moderate anemia.

Case V.—Observed from July 14 to October 8, 1910. There were three blood-cultures, with negative results. There was a history of articular rheumatism at the age of six years, and of palpitation and dyspnea since that time. The onset of the present illness occurred ten weeks before admission to the hospital, with pain in the thigh, swelling, and limping, all this being due to a ruptured embolic aneurysm of the femoral artery. The heart showed evidences of mitral and aortic insufficiency. The spleen was large (the spleen was particularly large in view of the fact that the boy was sixteen years of age and much undersized). There was a café-au-lait color to the face. The urine at first showed a specific gravity of 1020, later 1004 up to 1020; there were present erythrocytes and hyalogranular and granular casts. The blood count showed 15,200 leukocytes; 65 per cent. polymorphonuclears and a hemoglobin content of 20 per cent.; later the leukocyte count was 8400; polymorphonuclears 36 per cent., and the hemoglobin dropped to 17 per cent. The temperature was usually up to 102°. Death occurred from progressive anemia and a terminal pneumonia. The autopsy showed lesions of the mitral valve, chordæ tendineæ, and auricular wall, most of which were healed. In one part of the lesion there were found a few poorly staining cocci. The spleen weighed 510 grams (17 ounces); Malpighian bodies large.

Summary. Embolic aneurysm; marked splenic enlargement; renal phenomena; progressive anemia.

Case VI.—Case observed from June 26, 1911, to April, 1912. There were nine blood-cultures, with negative results. There was a previous history of rheumatism. The onset occurred three months before admission, with increase of a previously existing palpitation and dyspnea. There was frequent urination. The heart gave evidence of an aortic lesion. There was marked pigmentation of the face. The spleen was palpable. Numerous petechiæ occurred often. There were hemorrhages from the gums. There were tender nodes on the hands and feet on August 30 and October 4, and even as late as March 1. The lower sternum became distinctly tender under observation. The urine was at first grossly bloody, later erythrocytes were found microscopically from time to time. The specific gravity varied from 1020 to 1022; the amounts of urine were from 1100 to 2400 c.c.

The blood-examination showed a hemoglobin content of 39 per cent. at first; this then dropped somewhat lower, and a transfusion was done and the hemoglobin brought up to 55 per cent. It then rose to 61 per cent., but later dropped again. Leukocyte count was 10,400; polymorphonuclears, 81 per cent. The temperature was at first 101° to 102°, and later was occasionally as high as 101°, except just before crops of petechiæ developed. Death was due to progressive anemia and a terminal pneumonia. At the postmortem examination there were found calcareous and fibrous lesions of the aortic valve and aneurysms of the sinuses of Valsalva. The spleen was one and a half times the normal size; there was marked enlargement of the Malpighian bodies. The bone-marrow of the femur was red, and microscopically there were evidences of regeneration.

Summary. Pigmentation; renal phenomena; progressive anemia; tender nodes present long after the active stage of the disease was passed; hemorrhagic tendency; endocarditic symptoms.

Case VII.—Period of observation from April 16, 1911, to June 13, 1911. Cultures of the blood were not made during life, but at the postmortem examination the blood was found free from bacteria, as were also the cardiac lesions. There was a previous history of acute articular rheumatism and of cardiac disease. The patient suffered from dyspnea, pain over the heart, cough, and hemoptysis. The present illness began two weeks before the date of admission, with dyspnea, orthopnea, pains about the heart, cough, and expectoration, which was at times hemorrhagic. Examination showed insufficiency of both aortic and mitral valves. Spleen not palpable. No petechiæ. Urine showed a specific gravity of 1020 to 1026, and contained a trace of albumin. The quantities varied from 1400 to 1900 c.c. The temperature was usually up to 101° or 101.2°, later at one time up to 102°. The patient developed uremia and died suddenly, the explanation of the sudden death being unknown (the writer did not observe this case himself). At the postmortem examination there was found an adherent pericardium, a bacteria-free and partially healed lesion of the chordæ tendineæ, mitral valve, and auricular wall. The spleen weighed 570 grams (19 ounces), and contained infarctions.

Summary. Renal phenomena; marked splenic enlargement.

Case VIII.—Period of observation from July 17, 1911, to October 14, 1911. In this case the first five blood-cultures gave growths of the influenza bacillus, three later ones remained sterile, the first of these being taken on September 9. The patient was told two years before the onset of the present illness that he had endocarditis. For eighteen months he had had

pain in the ankles and feet, and had lost weight. On admission he complained of throbbing in the head, fever, and weakness. There were evidences of aortic insufficiency and mitral stenosis. At first the spleen was felt two fingers below the free border, and later four fingers below the free border. Petechiæ were present. The specific gravity of the urine varied from 1008 to 1024, later from 1011 to 1020; erythrocytes and hyaline and granular casts were present. Blood-count showed leukocytes, 6800; polymorphonuclears, 75 per cent.; hemoglobin, 64 per cent.; later the hemoglobin was 71 per cent., leukocytes 5800, and polymorphonuclears 42 per cent. The patient left the hospital some time after the blood was bacteria-free, and developed a marked progressive anemia and hydremia. At first the temperature was 104°, later not above 102°. The patient died of progressive anemia and exhaustion. An autopsy was not permitted.

Summary. Influenza bacillus infection; the case later became bacteria-free; progressive anemia; marked enlargement of the spleen.

Case IX.—Period of observation from August 8, 1911, to August 24, 1911. Two blood-cultures were taken, with negative results. The patient had previously been in the hospital from September 24, 1910, to October 15, 1910. On the first admission there was a history that the patient had had rheumatism since he was fifteen years old. Six months before the day of the first admission the patient was taken sick with fever and pain in various joints. He had marked sweats, occasional dyspnea, and palpitation and pain over the heart. The face was of a brownish color. Examination of the heart revealed mitral insufficiency and aortic insufficiency. The spleen was palpable one and a half fingers below the free border. Petechiæ and purpura both occurred. The lower sternum was distinctly tender. Urine showed a specific gravity of 1018 to 1020, a faint trace of albumin, some hyaline casts, and a few leukocytes. Blood examination at first showed leukocytes, 11,000; polymorphonuclears, 74 per cent.; later blood count showed leukocytes, 6000; polymorphonuclears, 74 per cent. On the day of admission the temperature was 103°, but after that did not rise above 100°. The patient died of cardiac insufficiency and uremia. Postmortem examination showed a bacteria-free calcified and ulcerative lesion of the aortic valve. The spleen weighed 210 grams (7 ounces); old infarctions were present; Malpighian bodies were prominent.

Summary. Pigmentation; endocarditic symptoms.

Case X.—Period of observation from November 27, 1911, to January 31, 1912. Three blood-cultures remained sterile. Patient was taken sick,

three weeks before admission, with dyspnea, cardiac palpitation, and nocturnal frequency of urination. There was marked brown pigmentation of the face. Examination of the heart revealed insufficiency of the aortic and mitral valves. The spleen was not palpable until shortly before death, when it was felt two fingers below the free border of the ribs. Petechiæ were present. The sternum was tender. Urine examination showed a specific gravity of 1016 to 1028, a trace of albumin, and occasional erythrocytes. Quantities of urine varied from 1500 to 2300 c.c. Blood-examination showed leukocytes, 9200; polymorphonuclears, 61 per cent.; later examination showed leukocytes, 7500; polymorphonuclears, 50 per cent.; hemoglobin, 65 per cent. The temperature was often up to 101° at first, and later 100° (except for rises due to an infection of the maxillary antrum and due to an acute otitis media). Death appeared to be due to embolism. Postmortem examination showed bacteria-free lesions of the aortic and mitral valves. The spleen weighed 420 grams (14 ounces), contained infarctions, and the Malpighian bodies were prominent.

Summary. Pigmentation; renal phenomena; embolism. This is one of the cases in which the patient passed large amounts of urine of high specific gravity.

Case XI.—Period of observation from December 26, 1911, to January 30, 1912. The patient had previously been in the hospital from March 18, to April 15, 1911. Three blood-cultures were taken, with negative results. On the first admission there was cough and palpitation. Petechiæ were present. Temperature 101°, later 100°. Two days before the date of the second admission there was pain in the right forearm, due to embolism of the brachial artery just before its bifurcation. Examination of the heart revealed insufficiency of the aortic and mitral valves. Spleen was not palpable. Petechiæ were present. The sternum was tender. The urine varied in amount from 900 to 1300 c.c., contained albumin and casts, but no erythrocytes. Blood examination showed leukocytes, 11,000; polymorphonuclears, 71 per cent. There is no record of a hemoglobin estimation, but the patient looked anemic. The temperature was at first 102°, later 101°. Death was due to cardiac insufficiency and anemia. At the postmortem examination there was found a bacteria-free healed lesion of the mitral valve and the chordæ tendineæ. The spleen weighed 135 grams ($4\frac{1}{2}$ ounces); there were infarctions present; Malpighian bodies were prominent.

Summary. Endocarditic phenomena and anemia.

Case XII.—Period of observation from December 28, 1911, to December 31, 1911. One blood-culture was taken, with negative result. The patient

had previously been in the hospital from March 24, 1905, to April 11, 1905, and from April 20, 1909, to May 1, 1909. There was a previous history of acute rheumatism. During the first two admissions he was supposed to be suffering from chronic endocarditis and rheumatism. At the time of the last admission he had been sick for four weeks, complaining of dyspnea, cough, cardiac palpitation, night sweats, and chilly sensations; he was very pale. There was marked sternal tenderness. The temperature never rose over 101°. The quantity of urine was at first 2700 c.c., and later dropped to 800 c.c. The urine showed a specific gravity of 1025 to 1028, later 1011. Blood-examination showed leukocytes, 10,000; polymorphonuclears, 78 per cent.; hemoglobin, 53 per cent. The patient died of cardiac insufficiency (and secondary renal insufficiency). Postmortem examination showed slight lesions of the aortic valve and marked lesions of the mitral valve, both bacteria-free. The spleen weighed 540 grams (18 ounces); there were infarctions present.

Summary. Moderately marked anemia; renal phenomena; marked splenic enlargement.

Case XIII.—Period of observation from January 10, 1912, to March 21, 1913. The patient had been at the hospital from January 10, 1912, to March 5, 1912. There were four blood-cultures, with negative results. On the first admission to the hospital the patient was suffering from chronic endocarditis, with pulmonary infarctions and a cerebral hemorrhage (as proved by the bloody character of the lumbar puncture fluid which was obtained at the time). When admitted on January 10, 1912, he gave a history of having had rheumatism eight years before, and since that time frequent attacks of pain about the heart and shortness of breath and also pains in the extremities. Two weeks before admission he was taken sick with a severe pulmonary hemorrhage; he was also suffering from pains in the region of the heart and left shoulder-joint, and marked weakness. He developed a brown color of the face under observation. There was sternal tenderness. The cardiac examination revealed a mitral insufficiency and stenosis and aortic insufficiency. He had repeated attacks of purpura. Tender nodes occurred in November, 1912, and the patient stated that he had had them already three years before. The urine varied in amount from 1700 to 2000 c.c.; the specific gravity was as high as 1030; there were hyaline casts present. During the period of observation there were several attacks of hematuria. Toward the latter part of the disease no erythrocytes were found. There were two attacks of cerebral embolism. The temperature was usually around 99°, except when embolic phenomena or pulmonary infarctions developed. The patient died of cardiac insufficiency. Postmortem examination showed old bacteria-free fibrous lesions of the aortic valve and ulcerative and fibrous lesions of the mitral valve, also

bacteria-free. The spleen weighed 240 grams (8 ounces) and was scarred from infarctions. The bone-marrow of the tibia was fatty (that of the femur could not be obtained).

Summary. Endocarditic symptoms (embolisms, purpura); pigmentation; renal phenomena; anemia. Special note is to be made in this case of the excretion of large quantities of urine and high specific gravity (the urine contained few or no formed elements when a large amount of concentrated urine was being passed).

Case XIV.—Period of observation from February 1, 1913, until the present time, the patient being alive and in little worse condition than when first seen. There were five blood-cultures made, all with negative results. The main features of this case were pigmentation of the face and marked tenderness of the lower sternum. The spleen was palpable at one time, and petechiæ were present in the conjunctivæ during the early part of the observation. The patient is in the hospital at the present time suffering from mitral insufficiency, with attacks of decompensation and acute bronchitis.

Case XV.—Period of observation from September 4, 1911, until the present time, the patient still being alive. One blood-culture was taken, with negative result. This patient suffering from insufficiency of the aortic and mitral valves. He showed marked pigmentation of the face and marked sternal tenderness. The spleen was palpable. He passed large quantities of urine, as high as 2350 c.c. The specific gravity of the urine varied from 1018 to 1027; there was a faint trace of albumin, and erythrocytes were found from time to time. The blood-examination showed leukocytes, 8800; polymorphonuclears, 48 per cent.

Case XVI. –Period of observation from June 4, 1912, until the present time, the patient being still alive. Two blood-cultures were made, with negative results. The patient gave a previous history of rheumatism. Two days before admission to the hospital he was taken sick with dyspnea and cardiac palpitation and pain. Face was markedly pigmented, and there was marked sternal tenderness. Petechiæ were found, and there were evidences of mitral insufficiency. He was becoming progressively more pale, and had lost weight. He was passing from 2800 to 2900 c.c. of urine; specific gravity, 1008 to 1020; some albumin, hyaline and granular casts, and erythrocytes. Blood-count showed leukocytes, 10,000; polymorphonuclears, 65 per cent.; hemoglobin, 50 per cent. The temperature ran from 101° to 102°, and once was 103°.

These last three cases appear to the writer to belong with great certainty to the group under discussion. Cases XV and XVI are

both working at the present time; Case XIV is up and about and is staying in the hospital because of the repeated attacks of bronchitis and asthma. These cases are identical with others that were picked out as clinically belonging in the group, and in which the diagnosis was confirmed by postmortem examination.

Case XVII.—Period of observation from August 22, 1912, to August 30, 1912. There was one blood-culture, with negative result. There was a previous history of rheumatism. Five weeks before admission to the hospital the patient complained of headache, fever, and chilly sensations. Examinations of the heart revealed insufficiency of the aortic and mitral valves. The patient appeared anemic. Petechiæ were present, and also marked tenderness of the sternum. Urine examination was practically negative. Blood-examination showed leukocytes, 12,000; polymorphonuclears, 76 per cent. The spleen was palpable two fingers below the free border. The temperature never rose above 100.6°. Death was apparently due to embolisms. Postmortem examination showed bacteria-free old lesions of the aortic and mitral valves. The spleen weighed 540 grams (18 ounces); there was marked hyperplasia of the Malpighian bodies; old infarctions were also present. The bone-marrow of the tibia was found to be red in color and microscopically showed changes found in bone-marrow regeneration.

Summary. Embolic phenomena; marked splenic enlargement; regeneration of the bone-marrow in the femur.

Case XVIII.—This case will not be discussed in detail at the present time. It is the case mentioned above which was suspected of belonging in the group in which there was not sufficient evidence at the postmortem examination to corroborate the clinical diagnosis. It will be described in detail at another time.

Case XIX.—Period of observation from September 16 to the present time, the patient being still alive. One blood-culture was taken, with negative result. This case is only suspicious and cannot be considered to surely be a case in the group. Three years before admission the patient was suffering from dyspnea and palpitation. There was marked brown pigmentation of the face. There was present a stenosis and insufficiency of the mitral valve and insufficiency of the aortic valve. Spleen was palpable. The sternum was distinctly tender. Quantities of urine varied from 700 to 950 c.c.; specific gravity ranged from 1010 to 1026; there was a faint trace of albumin, some leukocytes, and a few erythrocytes. Blood count showed leukocytes, 7200; polymorphonuclears, 63 per cent.; erythrocytes, 5,792,000; hemoglobin, 60 per cent. The temperature was practically normal.

Case XX.—Period of observation from September 17, 1912, to October 19, 1912. One blood-culture was made, with negative result. The patient was taken sick, one week before admission with dyspnea, pain in the chest, cough, with bloody expectoration, and swelling of the feet. He stated that he had had lesions that corresponded to the tender cutaneous nodules of subacute bacterial endocarditis three years before admission on three fingers of the left hand. The heart presented evidences of mitral stenosis and insufficiency and aortic insufficiency. The spleen was palpable. The patient looked anemic. The sternum was markedly tender. On September 13, the patient developed tender nodules on the thumb of the left hand, and he had had one on the right hand two weeks before. The quantity of urine passed was as high as 2400 c.c. a day; specific gravity varied from 1012 to 1016; erythrocytes were present, also granular and waxy casts. Blood-count showed leukocytes, 13,400; polymorphonuclears, 58 per cent. There was no record of any hemoglobin estimation, but the patient was evidently anemic. The temperature was up to 102° on September 8; after that it was usually around 99° or 100°, with occasional rises to 100.5°. The patient died of uremia. At the postmortem examination there was found a bacteria-free lesion of the aortic valve, slight in extent, and a more marked lesion of the mitral valve. The spleen weighed 450 grams (15 ounces); Malpighian bodies were prominent.

Summary. Occurrence of tender nodules in the bacteria-free period of the disease; anemia; nephritic condition.

Case XXI.—Period of observation from October 3, 1912, to December 6, 1912. Three blood-cultures were made, with negative results. This was a case which was taken by a number of observers to be one of Banti's disease. The patient, who was aged sixteen years, suffered for four months before admission from epistaxis, weakness, dyspnea, palpitation, swelling of the feet, and increasing pallor. Examination of the heart revealed mitral insufficiency. The spleen was large, being felt four fingers, below the free border. Petechiæ developed during the course of the disease. The color of the face was pale, with a café-au-lait tint. The urine was grossly hemorrhagic from time to time. The specific gravity ranged from 1012 to 1016, and once was 1026. The quantity was from 450 to 1950 c.c. It usually contained erythrocytes and leukocytes, and albumin in fair quantity. Blood-examination showed erythrocytes, 2,550,000; hemoglobin, 26 per cent., later 20 per cent.; leukocytes, 6200; polymorphonuclears, 62 per cent.; and later there were leukocytes 5200, and polymorphonuclears 56 per cent. The temperature at first rose to 103°, later it was only 101°. The patient developed edema of the lower eyelids, vomited repeatedly, and died in a profoundly uremic condition. At the postmortem examination

there were found lesions of the mitral valve and chordæ tendineæ. The spleen weighed 510 grams (17 ounces); the Malpighian bodies were prominent. The cultures made postmortem from the spleen and blood in this case showed an organism corresponding to the coccus generally found in these cases of endocarditis. Spreads made from the lesions in the heart showed absolutely no organisms. It is probable that in this case we are dealing with a case in which the lesions had become bacteria-free or nearly so only a short time before the patient came under observation. The cocci found in the spleen and blood at the time of the postmortem examination may have been thrown out from a few cocci left in some part of the vegetations or from some organ in the body where they had remained in latent condition and had then multiplied after or shortly before death. The fact that no cocci could be found in the vegetations is quite definite proof that the patient was becoming free from the bacterial infection because, as a rule, in all cases in which cocci are found in the blood during life or in postmortem examination the vegetations are full of cocci.

Summary. Marked splenic enlargement; marked renal phenomena; severe anemia; some pigmentation of the face developing under observation.

Case XXII.—Period of observation from December 3, 1912, to December 11, 1912. Only one blood-culture was taken in this case, and in that a typical pneumococcus was found. The case, nevertheless, belongs in the group of cases which are undergoing spontaneous healing, for reasons which will be given when the postmortem findings are discussed. This patient, who was aged fifteen years, stated that she had had, for five years, frequent attacks of cardiac palpitation and dyspnea. The feet were swollen on frequent occasions. Three weeks before admission she was suddenly seized with cardiac palpitation and weakness, and took to bed. There were cough and expectoration, and these have continued until the time of admission to the hospital. For the last eight or nine days before admission she had been jaundiced. Examination of the heart revealed the presence of mitral stenosis and insufficiency and aortic insufficiency. The spleen was palpable and petechiæ were present. The quantities of urine were 500 to 600 c.c.; specific gravity, 1020 to 1022; hyaline and granular casts, and erythrocytes were present; bile was easily demonstrable. Blood-examination showed hemoglobin 48 per cent. The temperature remained around 100° until December 5, when it rose to 105°; on the following days it was up to 103°. This rise of temperature was due to a lobar pneumonia, of which the patient died. At the postmortem examination there was found a bacteria-free lesion of the auricle and mitral valve. The spleen was twice the normal size, and there were old infarctions

present. The kidneys showed typical embolic glomerular lesions, all in the healed state. Because the lesions in the heart were rather old and bacteria-free, and because the embolic lesions in the kidney were all completely healed, and there was practically no fever up to the time that the pneumonia developed, the writer is of the opinion that the presence of pneumococci in the blood was due to a lobar pneumonia developing in a person who was in the bacteria-free stage of subacute bacterial endocarditis.

SUMMARY. Marked anemia; renal phenomena; terminal pneumonia.

DISCUSSION

DR. HENRY SEWALL: Does the temperature curve have any distinctive features in these cases?

DR. LIBMAN: The temperature is not high in these cases; it is much lower than in acute forms of endocarditis.

Signs of endocardial mischief, with low temperature and pigmentation of the face, are the distinguishing features of the clinical group under consideration.

A CLINICAL STUDY OF HYPERTENSIVE CARDIO-VASCULAR DISEASE[1]

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Contents

I. Material studied.
II. Sex distribution.
III. Proportion of living and dead.
IV. Age distribution.
V. Distribution by height of systolic blood-pressures.
VI. Symptoms associated with hypertension.
    1. Cardiac symptoms.
    2. Renal symptoms.
    3. Cerebral symptoms.
    4. General symptoms.
    5. Symptoms depending upon other diseases.
VII. Causes of death and the relation of early symptoms to them.
    1. Distribution by causes of death.
        a. Sex distribution.
        b. Age in relation to causes of death.
        c. The relation of blood-pressure to causes of death.
    2. Distribution by symptoms.
        a. The relation of blood-pressure to early symptoms.
        b. The relation of early symptoms to causes of death.
    3. The relation of early symptoms in deceased and living groups.
VIII. Additional data from histories and physical examinations.
    1. Apoplectic attacks.
    2. Anginal attacks.
    3. Cardiac arrhythmias.
    4. Evidence of cardiac hypertrophy.
    5. Accentuation of the aortic second sound.
    6. Evidence of arteriosclerosis of the peripheral arteries.
    7. Urinary findings.
        a. Albumin and casts in the urine.
        b. Specific gravity of the urine.
    8. The relationship of diabetes to high blood-pressure.

[1] From the Department of Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York City.

IX. Duration bearing on duration of disease.
  1. Duration of life from first symptom. Duration of illness in relation to causes of death.
  2. Duration of life after finding high blood-pressure.
X. Etiology.
XI. General considerations.
XII. Conclusions.

The study here reported was begun a year and a half ago. It was undertaken primarily with a view of determining whether a critical analysis of a large group of histories of persons with high blood-pressure would disclose any hitherto unsuspected relations between the symptoms or evidences obtained by objective examination and the subsequent course of the disease, upon which more exact prognosis might be based. The results of the study were reported in part before the Section on Medicine of the American Medical Association in 1912.[1] During the year that has elapsed since then it has been possible to obtain accurate information about a much larger proportion of this group of patients.

I. Material Studied. The material studied consists of the case histories of private patients examined by my father or myself during a period of approximately nine years, from the time when I began to make routine blood-pressure observations with the wide armlet in 1903 until June, 1912. These histories are almost entirely the records of persons belonging to the well-to-do classes of society. A number have been observed personally over the whole period, but for the most part the information as to the subsequent history and the date and cause of death was obtained from the family physician originally referring the case or from his successor in charge of the patient. It is a pleasure to acknowledge the hearty coöperation received from many physicians throughout the country. Their careful answers to the inquiries made give this study much of its value.

An analysis of such a type of material has obvious defects as well as advantages. It is clear that the diagnoses of the causes of death, almost all unchecked by autopsy, have only such a degree of

[1] Janeway, Theodore C. A Study of the Causes of Death in One Hundred Patients with High Blood-pressure, Jour. of the Amer. Med. Assoc., 1912, lix, 2106.

probability as one may expect from a group of general practitioners. However, this source of inaccuracy was greatly minimized by the grouping which I adopted. On the question sheet sent to the physician I asked whether death had been by cardiac insufficiency, uremia, apoplexy, acute edema of the lungs, gradual anemia, pericarditis, by complicating acute infection or some unrelented disease, with a request for details. The weakness of a method of this kind is revealed by the fact that in only a single case, and that a patient seen by myself in his last illness, was pericarditis diagnosed. For the investigation of pericarditis in patients with hypertension only a study of autopsy material is permissible. Of the other diagnoses, the majority are clinical rather than anatomical, and they may for the most part be accepted at their face value. Only in the discrimination between certain types or uremia and apoplexy is decision difficult. It is highly probable, and this was well brought out by Cabot's[1] study of three thousand autopsies, that apoplexy is the real cause of a certain number of deaths set down to uremia. In the consideration of my statistics, therefore, it must be assumed that the number of patients reported as dying of apoplexy is almost certainly below the true number, and that the total deaths credited to uremia contain the difference and are therefore in excess of the facts. As in their other relations, these two groups show many similarities, they can often be considered together, and the error then falls out of consideration. A small number of patients were said to have died "suddenly," without further details being given; no attempt has been made to classify these deaths further.

Questions were asked as to the existence or non-existence of certain clinical symptoms; these were an additional check upon the diagnosis of the cause of death. The only statistical use which I have made of the information obtained from other physicians as to subsequent symptoms has been in the study of the incidence of hemiplegic attacks. The errors here will all be errors of omission.

For the purpose I had in view it seems to me that the advantages of a study of such private patients far outweigh the defects. The

[1] Cabot. Diagnostic Pitfalls Identified during a Study of Three Thousand Autopsies, Jour. Amer. Med. Assoc., 1912, lix, 2295.

facts most necessary were the first symptom and the prominent early symptoms exhibited by the patient. To obtain reliable information on these points requires both an intelligent patient and a physician experienced in taking histories with reference to the particular points involved. It is evident that the conditions were fulfilled from the side of the patient. So far as the other factor enters into the situation, the vast majority of the histories were taken by myself and the remainder by my father. The earlier ones are less complete in their information on some points than those taken after I had begun to make my case records with the definite object of their subsequent scientific utilization. Here, again, undoubted errors of omission exist, and it is probable that some of the symptoms of a minor nature are less completely represented than more conspicuous symptoms, such as severe dyspnea, anginal attacks, or edema of the lungs. Apart from this, the omissions are probably distributed evenly throughout the earlier histories, and they will not lead to substantial inaccuracies.

The physical examinations included in these statistics were also made by my father or myself. In this way, any errors due to the personal equation are practically a constant throughout all observations, and can thus be neglected. For a satisfactory study of prognosis, only such private material can be used. A study of symptoms from hospital records is so defective as to be of little value. In the first place, ward patients are largely unintelligent and unobservant, and early symptoms are apt to pass unnoticed. In the second place, hospital historians are inexperienced and vary greatly in their ability and the care with which they interrogate the patients. In this way a series of records running over any considerable period of years would be uneven in character, the personal equation being a wholly unknown factor. Finally, it would be practically impossible in our hospitals to obtain more than a fraction of the subsequent information which I have been able to collect about these patients. If further argument is needed in defence of the use of such clinical material lacking autopsies, for a study the aim of which is chiefly prognosis, I cannot do better than to quote the first student of the hypertension problem, Richard Bright:

"Another very important question is the length of time which this disease may exist in the constitution before it runs to its last final period, and although our experience in the hospital is great, the point or duration is yet undetermined; for, with all the advantages which a hospital affords for the multiplied accumulation of facts, there are some points on which the information derived from its wards is defective and even apt to be erroneous; and among these may be reckoned one of great importance, the probable duration of life, under any disease. If a case is much relieved, the hospital physician loses sight of it, and in all probability sees it no more; knowing nothing of future relapses or of the ultimate results. On the other hand, a very large proportion of his cases arrive at the most advanced stage of the respective disorders; the circumstances have been such as to render them inattentive to the earlier indications of disease; and it is only when they can no longer pursue their laborious occupations that they are driven, too late, to seek relief. Hence the physician is liable to form a wrong estimate of the progress of the disease under more favorable circumstances; and it is necessary to correct his views by a comparison with the history and results of private practice.

"There has not yet, perhaps, been sufficient time, since this disease of the kidneys first attracted attention, to say to what extent life may be prolonged while the body is under its influence; but I believe, with care, its fatal effects may be kept at bay, and a hazardous life may be protracted for many years. Should that care be neglected, the chance of life will be greatly diminished."[1]

The total number of my case records for the nine years was 7872. Of these, 870, or 11.1 per cent., showed at some time a systolic blood-pressure of 165 mm. Hg. or over. I have chosen to consider only pressures above 160 mm. because there is now substantial unanimity of opinion that, taken with the wide arm-band, such pressures are always pathological. The extensive life insurance statistics of Woley and Fisher bear this out. I have always been convinced of it.[2] Cook[3] believes that 150 mm. will eventually

[1] Bright, Richard. Cases and Observations illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, Guy's Hospital Reports, 1836, i, 338.
[2] Janeway, Theodore C. The Clinical Study of Blood Pressure, New York, 1904.
[3] Cook. Blood-pressure in Prognosis, Med. Rec., 1911, lxxx, 959.

prove the upper limit of normal systolic arterial pressure, and I am inclined to believe him right, when readings are made with care to exclude temporary factors. Where patients are seen but once, one cannot be certain of this. Therefore, it is wise to exclude from consideration all patients who have not had a systolic blood-pressure of 165 mm. or over. In addition, systolic pressures as high as 165 or 170 mm. are not infrequent in patients with severe cardiac insufficiency, in exophthalmic goitre, and at times in aortic regurgitation, and are seen transiently without a satisfactory explanation. My total group of 870 patients includes a number of instances of what seemed to me temporary hypertension, not associated with the type of disease which is the subject of this paper. These cases were eliminated from consideration, and no attempt was made to obtain information about them.

While I have diastolic readings in practically all cases, they were by different criteria at different stages of the study, and are not strictly comparable with one another. In addition, the consideration of them would so much further complicate the large amount of statistical work embodied that I have omitted the diastolic pressure entirely from consideration.

Of the remaining cases, I was able to obtain definite information up to June, 1912, of 458. This group of 458 patients forms the basis of the statistical analysis which follows.

II. Sex Distribution. The total group of 7872 patients contained 4660 men and 3212 women, the percentage of men being 59.2 and of women 40.8, or 18.4 per cent. more men than women. This preponderance of men is probably largely dependent upon the fact that neither my father nor I have ever engaged in obstetrical or gynecological practice. The group of 870 patients with high pressure contains 543 men (62.4 per cent.) and 327 women (37.6 per cent.), a preponderance of 24.8 per cent. for the men.

The group of 458 patients that I have considered as having had permanent hypertension was made up of 307 (67 per cent.) men and 151 (33 per cent.) women. The preponderance of men over women is, therefore, 34 per cent., as against 18.4 per cent. for all the patients observed during the nine-year period. Subtracting the latter figure from 34 per cent. leaves 15.6 per cent. as the apparent

extra incidence of hypertensive disease in the male sex. Even taking the group of 870 patients who had at any time a blood-pressure of 165 mm. or more, the male preponderance by the same calculation is 6.4 per cent.

It seems clear, therefore, that the diseases associated with persistently high arterial pressure are decidedly more common in men than in women. In all the analyses, figures for the men and women have been tabulated separately and separate curves have been drawn for the two sexes.

III. Proportion of Living and Dead. Of the 458 patients, 212 (46.3 per cent.) men and women had died by June, 1912, and 246 (53.7 per cent.) were living. Separating these by sexes, the figures are as follows:

Table I.—458 Patients with High Blood-pressure

	Whole No.	Living. No.	Living. Per cent.	Deceased. No.	Deceased. Per cent.	Preponderance. Per cent.
Men . . .	307	144	46.9	163	53.1	6.2 deceased
Women . .	151	102	67.5	49	32.5	35.0 living
Difference .			20.6		20.6	

This table brings out several striking facts: (1) the number of men who had died by the arbitrary date chosen for the completion of the statistics, June, 1912, was 6.2 per cent. in excess of the number still living; (2) for the women, the excess was 35 per cent. in the other direction; many more women were living than had died. In the same way it is seen that 20.6 per cent. more men than women had died during the same period.

It is hardly possible that accidental circumstances or differences in the distribution of men and women between earlier and later years of the nine-year period could account for so extreme a variation. I have always had the impression that the expectancy of life in women with arterial or renal disease was greater than in men. This analysis gives such impressions an objective foundation in fact. I am inclined to attribute this preponderance to the difference in mode of life and especially in the demands made upon men and women by their social environment in a group of such private patients. Women are far better able to shield themselves from

influences leading to sudden rises of blood-pressure with the attendant danger of apoplexy and cardiac overstrain. In general they can accommodate themselves more easily to the type of life best fitted to limit the progress of arterial and cardiac disease.

IV. Age Distribution. For 446 of the patients the ages were known. These ages, grouped by decades, are shown in graphic form in Chart I.

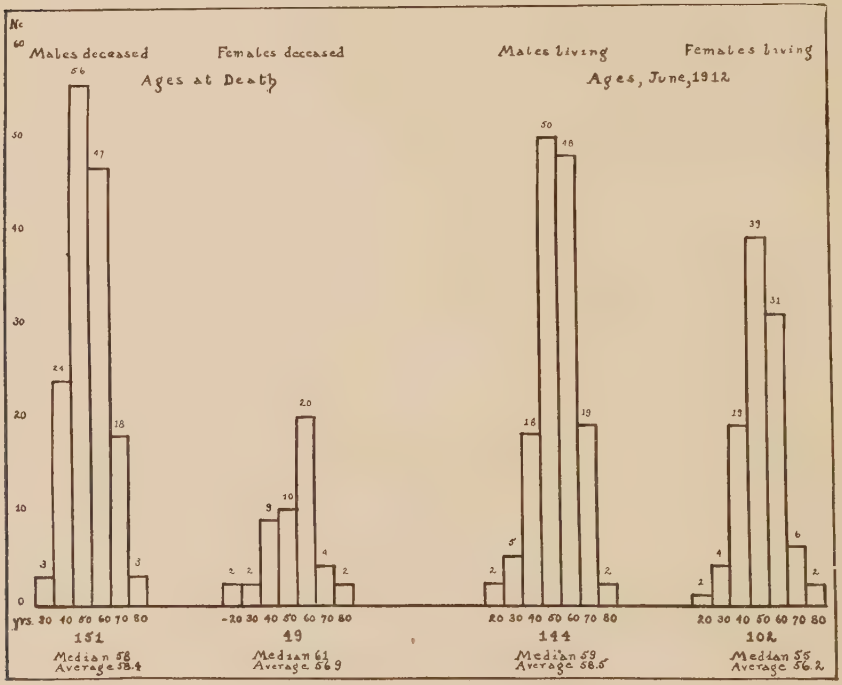


Chart I.—Ages of 446 patients with blood-pressures of 165 mm. and over.

It is clear that the three decades from forty to sixty-nine years contain between 80 and 90 per cent. of all the cases. The exact proportions are as follows:

Table II.—Ages between 40 and 69 of 446 Patients in Percentages[1]

	Males.	Females.
Deceased	84.1	79.6
Living	80.6	87.3

[1] The percentages are computed on the basis of the totals in each case, *i. e.*, total number of deceased males, etc.

For every group, the next largest number of cases falls in the period of seventy to seventy-nine years. The number of patients over eighty is greater than the number below thirty. This is, of course, in general conformity with all vital statistics: apoplexy, Bright's disease, and heart disorders, under one of which categories these cases would be reported, show their greatest incidence above the fortieth year. On the other hand, these ages I believe are considerably higher than would be found in a similar number of patients with high blood-pressure dying in hospitals. Bright[1] tabulated the ages at death in seventy-four of his patients as follows:

TABLE III.—Bright's Classification of Ages at Death of 74 Patients

Ages.	Number.	
8 years	1	
Under 30 years	19	
30 to 40 years	16	
40 to 50 years	21	
50 to 60 years	13	51.4%
Over 60 years	4	
	74	

The difference between the two sets of figures is very startling; 48.6 per cent. of his patients died before reaching the fortieth year. In commenting upon these cases, Bright remarks:

"The youngest, whose age is given, is only eight; and there is one advanced to seventy-three; showing, therefore, that neither youth nor age is exempt from this disease, but that it has cut off the greater part of its victims before the middle period has been attained."

Bright, of course, was dealing with cases of nephritis, acute or chronic, terminating fatally in a large London hospital. These patients did not all have hypertension, as is clear from his figures as to the proportion with hypertrophied hearts. They, therefore, represent some patients with the type of disease which I am considering, together with a group of the less chronic forms of nephritis. Even then the very large proportion of individuals under forty years of age leads one to ask whether the disease from

[1] Bright, Richard. Cases and Observations Illustrative of Renal Disease, Accompanied with the Secretion of Albuminous Urine, Guy's Hospital Reports, 1836, i, 400.

which all these young adults died has not become distinctly less common during the past seventy-five years, owing to changes in the hygiene and habits of the community. It is difficult for me to resist the impression that this is true.

I know of no published statistics with which mine are really comparable. Smith[1] in 2000 consecutive autopsies at the Massachusetts General Hospital found 442 showing some arteriosclerosis. Of these, 21.3 per cent. were between forty and fifty years of age, 29 per cent. between fifty and sixty, and 25.8 per cent. between sixty and seventy, in all 76.1 per cent. The number of cases dying at seventy and over was double the number dying below forty years of age. In my statistics, however, there were three times as many of the aged as of those dying before the fifth decade. The difference is mainly made up by the large number of patients in his group (19) with aneurysm, showing an average death at forty-five years, as against an average age of his cardiorenal group at nearly fifty-five years, of his cerebral group dying of apoplexy at sixty years, and of the patients dying of gangrene at sixty-five years. For the most part the aneurysm cases would not have shown hypertension during life.

I wish to call attention to the discrepancy between the average ages of the men and women in my statistics and the median for the ages of the two groups. There seems no question that the median or middle point is much more important from the standpoint of prognosis than the average age; the median indicates a real tendency. From it, it is evident that the probability of living beyond fifty-eight years for the men and sixty-one years for the women is as great as the probability of dying before that time. It also seems clear to me that, for a large proportion of these individuals, the disease of which high blood-pressure was a symptom could not be looked upon as materially shortening the span of life to which man has a traditional claim, but rather that it was for them an incident of growing old.

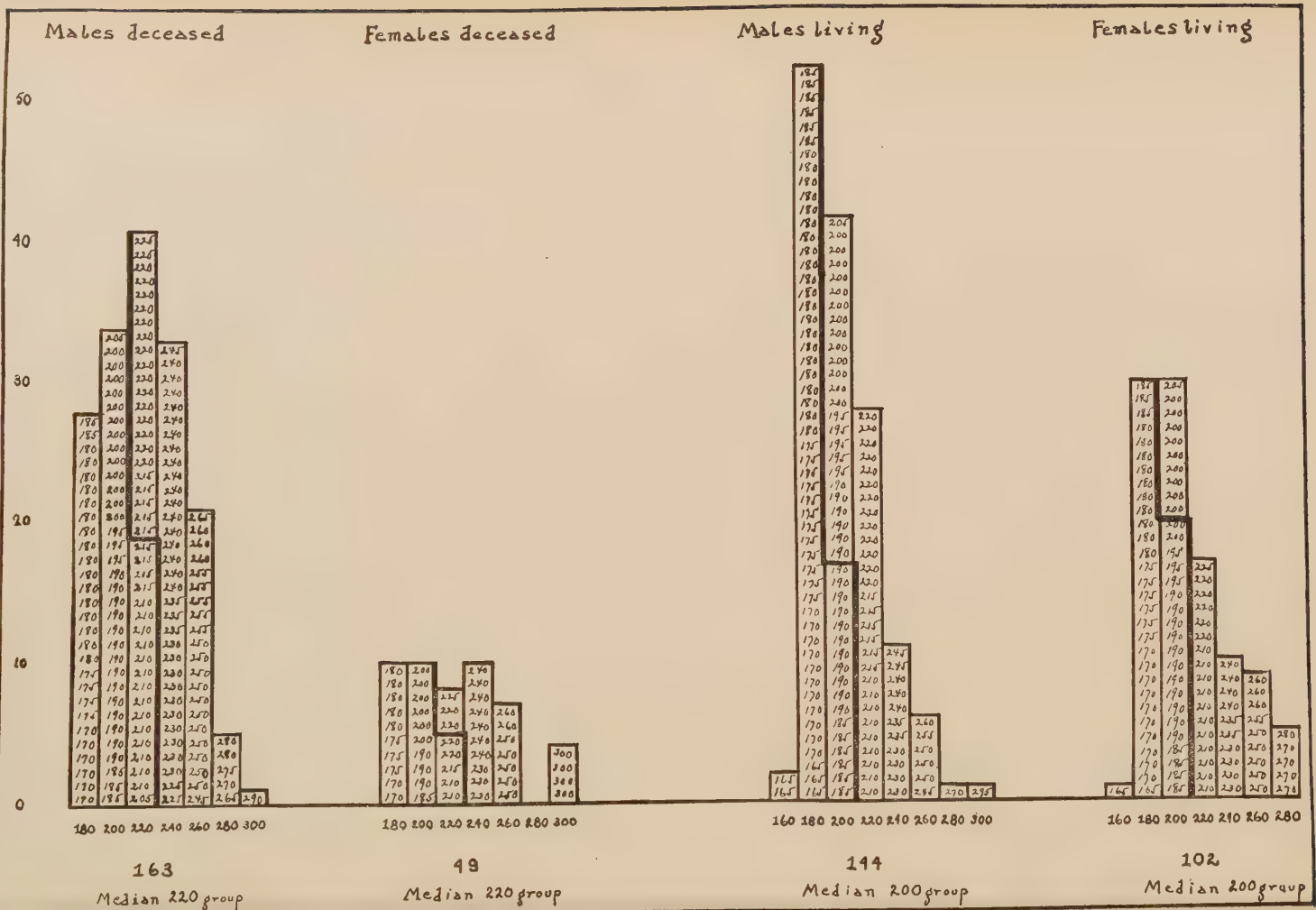
The difference of six years between the median for the women living and deceased is difficult to explain. It suggests the need for

[1] Smith, W. H. Age in its Relation to Arteriosclerosis and Death from Arteriosclerosis, Massachusetts General Hospital Report, 1908, ii, No. 1, p. 185.

reserve in interpreting the high percentage of living women as an evidence of a more favorable course of the disease in the female sex. Such ages at an arbitrary period in the course of a disease mean little in themselves. If it were possible to tabulate a sufficient series of cases terminating at or before a certain age, rather than patients living or dead at a particular date, much more definite conclusions would be warranted.

V. Distribution by Height of Systolic Blood-pressures. The study of the height of the blood-pressures has been the most disappointing part of this work. The blood-pressure naturally varies from day to day and from year to year. The only reliable figures that I could command were my own observations at the time of examination, sometimes one reading for a patient, sometimes many readings extending over a long period of years. I have in every case taken the highest recorded systolic pressure, and have arranged these pressures in groups, in different ways, in the hope that some intelligible curve of tendency might be evident. The attempt at grouping at once showed what seems to be well known to statisticians, namely, the tendency of the mind to select the nearest multiple of ten where there is a choice between it and the five below or above. This I have found to be true in surveying my blood-pressure readings. For this reason, in the final groupings shown in Charts II, III, and IV, the readings have been redistributed to make groups at 20 mm. intervals of pressures from 160 up. Chart II shows the entire number of 458 patients thus grouped according to systolic blood-pressures, with the actual readings given in the columns.

It is evident that the lower pressures predominate in the living as compared with the dead groups, the median blood-pressure for the former being about 200 mm. and for the latter 220 mm. The same tendency is shown in Charts III and IV, in which the blood-pressure readings in relation to the number of cases are shown in the form of curves. It is of considerable interest to note in Chart III of the deceased patients that as many showed a blood-pressure of 220 mm. and higher as a lower figure, both men and women. Considered from any standpoint, there seems to be no tendency for lower blood-pressures among the women than among the men.


Males deceased
Females deceased
Males living
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10
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30
40
50
180 200 220 240 260 280 300
180 200 220 240 260 280 300
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102
Median 200 group

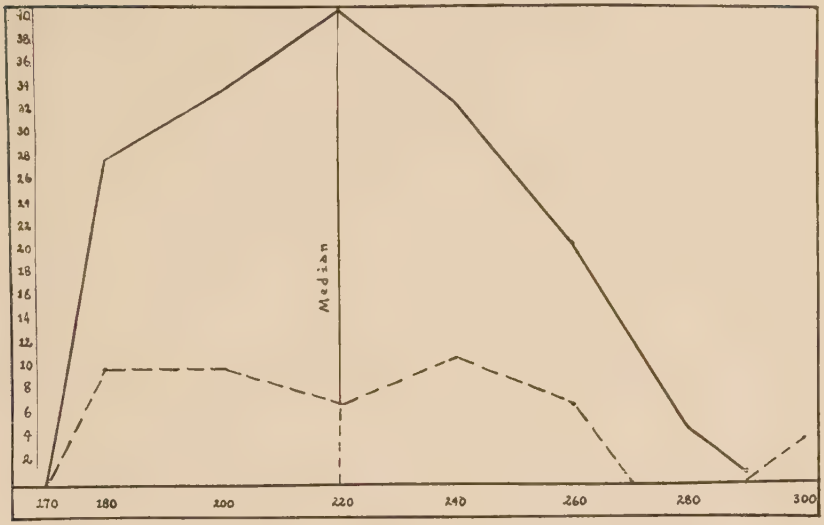

CHART III.—Blood-pressure readings—deceased; solid line, males, 163; broken line, females, 49; total, 212.

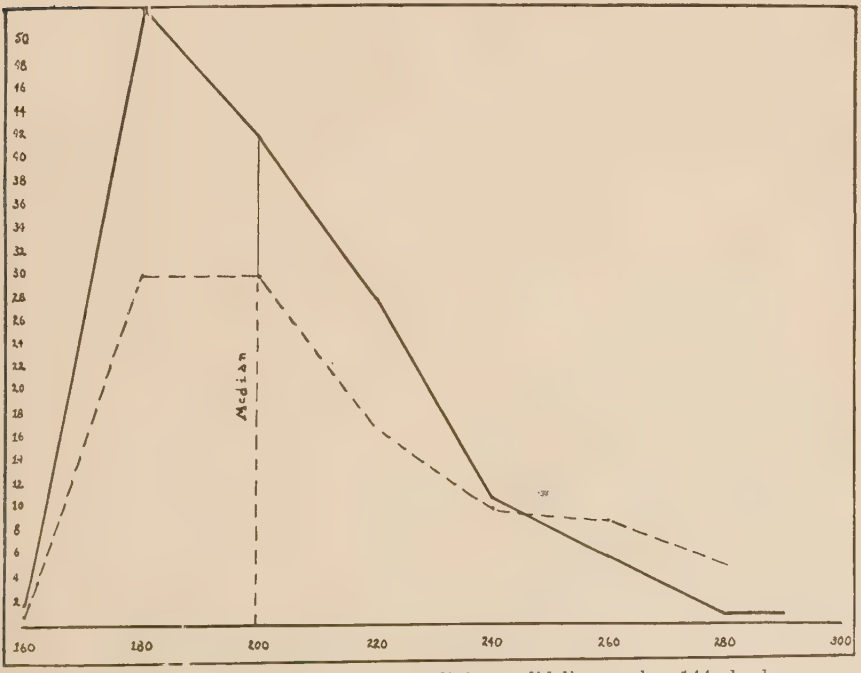

CHART IV.—Blood-pressure readings—living; solid line, males, 144; broken line, females, 102; total, 246.

In fact, a much higher proportion of women, both living and dead, showed very high readings, 280 mm. and over.

A tabulation of the duration of life as it was found in 197 of the deceased after my examination of the patient, arranged by blood-pressure readings, is shown in Table IV.

The patients dying in less than a year were for the most part seen during their terminal illness and are of no value for this purpose. The instructive groups are those that lived for six years and over; not a single one of these patients had a blood-pressure reading below 200 mm.

It does not seem to me that any very definite prognostic conclusions can be drawn from the height of the blood-pressure. I am confirmed in this opinion by certain individual cases where extraordinarily high pressures were tolerated for six and more years, while other patients with very moderate elevation of pressure died in a much shorter time. While, therefore, the medians of the living and the deceased groups do seem to show a certain unfavorable significance of blood-pressures above 200 mm., I consider the height of the blood-pressure a minor factor in determining the expectancy of life.

VI. Symptoms Associated with Hypertension. For many years I have interrogated patients with special care in the endeavor to determine the earliest symptoms associated with cardiovascular and renal disease. These patients so frequently seek medical aid for the first time when in the advanced stages of their malady, that it has seemed to me of particular importance, in dealing with an intelligent group of patients, to trace back as far as possible to the first deviation from accustomed health. In many instances the task is impossible, because of preceding disease of some other nature, during which the hypertensive cardiovascular disease has developed as a sequel or a concomitant. This is particularly true of diabetes in elderly subjects. With careful study, however, one may often find definite symptoms of failing cardiac reserve force, of urinary disturbance, of circulatory brain disorder, or a still less definite sense of fatigue, remembered as originating years before the physician was consulted. A knowledge of these early symptoms is so important for the recognition of the existence of serious organic

TABLE IV.—Duration of Life of One Hundred and Ninety-seven Deceased Patients after Examination and Finding of High Blood-pressure

Duration.	Systolic Blood-pressure Readings in Millimeters.														Total.
	165 to 170	175 to 180	185 to 190	195 to 200	205 to 210	215 to 220	225 to 230	235 to 240	245 to 250	255 to 260	265 to 270	275 to 280	285 to 290	295 to 300	
Less than 1 year	1	17	9	10	7	15	13	12	8	3	2	2	0	1	100
1 year	3	5	5	4	3	5	0	7	6	1	1	0	0	1	41
2 years	0	2	1	3	0	3	1	3	2	1	0	0	0	0	16
3 years	0	4	3	1	2	0	2	1	1	1	0	0	1	0	16
4 years	0	1	3	3	1	2	0	1	0	2	0	0	0	1	14
5 years	0	0	0	0	0	1	1	2	0	0	0	0	1	0	5
6 years and over	0	0	0	0	1	1	0	2	0	0	0	0	0	1	5
	4	29	21	21	14	27	17	28	17	8	3	2	2	4	197

disease, that I feel justified in enumerating the symptoms that have appeared in this group of patients. They group themselves naturally in certain categories.

1. *Cardiac Symptoms.* The most important numerically are the cardiac symptoms. Dyspnea stands first, beginning either with some shortness of breath on exertion, or a paroxysm apparently coming out of a clear sky. The severest grade, of course, is seen in connection with the somewhat rare attacks of acute pulmonary edema. Anginoid pain on exertion has been characteristic of a considerable number of patients. Some have had purely subjective cardiac disturbances, palpitation or extrasystoles, of which they were unpleasantly aware, less often other arrhythmias. Some had paroxysmal tachycardia for years before death. Edema of the legs, while a common late symptom, frequently appeared early, and in two patients was the initial symptom.

2. *Renal Symptoms.* Polyuria, nocturia, or frequency of urination were admitted by a very large number of patients. In many cases it was not possible to determine whether nocturnal frequency indicated nocturnal polyuria or not. The elderly men with hypertrophied prostates naturally complained of nocturia, and it was not possible in them to determine from their story when polyuria was superadded. The symptom is, I believe, of great importance, especially marked degrees of polyuria. In the subsequent tabulation it has been necessary to group all those complaining of nocturnal frequency in the same category, though it is fairly certain that in a number this symptom must have been due to local causes. Oliguria was practically impossible to determine from the patient's statement. Albumin and casts were discovered incidentally as the first evidence of disease in twelve of the deceased men, and in no women. This illustrates well the advantage of life-insurance examination for the early detection of chronic disease.

The striking absence of onset with general edema of nephritic type indicates, as clearly as anything, the wide divergence of these patients from patients with high blood-pressure as found in hospital wards. I believe, however, that were the histories of our hospital patients taken with the same degree of care, some symptoms would be found antedating the onset of general anasarca in almost all cases.

3. *Cerebral Symptoms.* Cerebral symptoms were noted early by many patients. Headache was the most frequent. The study of the significance of headache has been beset with many complications, for a surprisingly large number of these patients have been subject to migraine throughout life. Some patients have been able to name a definite date when the character of the headache changed completely; others have noted a greater severity of the paroxysms. In still others, headache has appeared for the first time with the onset of the vascular disease. So commonly have patients described to me a particular kind of headache that I have almost come to look on it as a typical nephritic or hypertensive symptom. This headache is one which appears on awakening, or wakes the patient during the early morning hours, has its greatest intensity before arising, and passes away either immediately after breakfast or during the course of the morning, to reappear in the same manner, day after day, for considerable periods. The intensity of the pain and its location have varied somewhat, the most severe being similar to bad migraine, and in a few cases it is attended by nausea and vomiting. The time of onset and offset has been the characteristic of greatest constancy. Throbbing has accompanied it in some cases, but not in all. I shall allude to this type hereafter as "typical" headache. Sensations of fulness or pressure in the head have been noted by many patients who did not suffer from actual headache.[1]

[1] The following case histories illustrate this type of headache and are of particular interest.

Case No. 44, aged forty-five years, male, designer. Father died of Bright's disease, mother of apoplexy. Consulted Dr. E. G. Janeway on February 23, 1905, because of headaches for ten years. The headache regularly began in the morning on arising and lasted until noon. It was occipital and radiated to the vortex. During the past one and a half years he had lost 35 pounds in weight. For a year he had had transient attacks of aphasia and for two months had gotten up once every night to urinate. He had no cardiac symptoms whatever. On physical examination he showed slight cardiac hypertrophy, extreme accentuation of the aortic second sound, moderate peripheral arteriosclerosis, a blood-pressure of 255 systolic, 170 diastolic. The reflexes were generally increased, with a slight ankle-clonus on the right. The urine was 2160 c.c., specific gravity 1.015, a moderate amount of albumin, at times a few hyaline and granular casts. He died in October, 1906; the cause of death could not be determined.

Case No. 41, aged thirty-seven years, brother of the preceding, piano-tuner. Consulted Dr. E. G. Janeway on April 7, 1908, because of headache. For seven or eight years he had been subject to occasional occipital headaches. For three months the headache had come daily, beginning in the occipital region and radiating forward to the frontal region. The pain was usually a dull ache, at times a sharp,

Dizziness or severe attacks of vertigo have occurred with or without headache, also drowsiness and insomnia. Apoplectic attacks, varying in severity from transient aphasia to complete hemiplegia, have characterized a group of moderate size, with a definite tendency to recur in the same individual, as I shall bring out later. In eight patients, an apoplectic attack was the first symptom discoverable. Onset with a convulsive seizure was a great rarity. In one case, however, four years intervened between the initial uremic convulsion and death.

cutting pain in the occiput; no throbbing. The milder attacks began at 2.00 A.M., passing off toward morning; the worst ones lasted all day. The headache awakened him out of sleep almost every night. He had no relief from any drug except an acetanilide mixture, which he had taken in large quantities. For one year he had been getting up frequently at night to urinate and had been losing weight rapidly. Because of persistently negative urine examinations, his kidneys were exonerated from blame. On physical examination he showed a moderate hypertrophy of the heart, with accentuated aortic second sound, arteries full, tense, but without marked thickening; the blood-pressure was 230 systolic, 160 diastolic, the pulse 100, regular. The reflexes were normal. The ophthalmoscopic examination showed slight haziness of the disk outline, fulness of the veins, one pigmented area in the right retina, otherwise nothing. The urine was 2200 c.c., specific gravity 1.018, without albumin but with a rare hyaline cast. On July 5, 1908, following a sea bath he developed intense headache, shortly afterward became delirious, then unconscious, and died in coma at noon the next day.

Case No. 77, aged thirty-nine years, male, physician. No family tendency. Had diphtheria at thirteen, severe cellulitis of arm at twenty-eight, no other infections. Consulted Dr. T. C. Janeway on November 7, 1911. Four years before, a small amount of albumin and a few casts had been found on life-insurance examination, but his general health was perfect. Eighteen months before, he developed what seemed ordinary sick headache once a month. The headache would begin at about 4 A.M., becoming severe; it was generally associated with vomiting and would last until the next night's sleep brought relief. The albuminuria increased somewhat, casts became more abundant, and a few red cells were present. The headaches gradually increased in frequency and were usually relieved by vomiting. During the summer of 1911 he exercised hard. The headaches were no worse. For a year or two he has had to urinate once every night. For two weeks before examination great polyuria (five or six times at night). He had absolutely no cardiac symptoms. He had a good appetite, but lost ten pounds in weight. On physical examination he showed a slightly forcible apex impulse in the fifth interspace, four inches from the midsternal line, practically normal sounds, arteries small, thickened, blood-pressure 165 systolic, 110 diastolic, pulse-rate 80, regular. Normal reflexes, no edema, normal fundus oculi. The urine (twenty hours) was 1060 c.c., specific gravity 1.016, contained considerable albumin, epithelium, and granular casts, red-blood cells, and many leukocytes. Subsequent history: On a restricted diet, occasional purgation, and sweat baths, he did well for a time, but had an attack of acute gout in March, 1912. By July, the headaches became very severe, about five days in the week, practically always in the early morning hours. The blood-pressure rose to 210 systolic, 130 diastolic. Hypertrophy of the heart became more evident. He lost some flesh. In September, after repeated headaches, most intense in the occipital region, he developed vomiting, gradually became irrational, the blood-pressure reached 255 millimeters at the highest. He sank into a state of chronic uremia, with high blood urea, and died after forty-eight hours of coma, with rising temperature and falling blood-pressure.

Failure of eyesight as an initial or even an early symptom was noted by thirteen of the deceased patients and thirteen of those are still living. My general impression of hospital and dispensary patients, without definite figures to go by, is that in them ocular disturbance is a distinctly less frequent initial symptom. This could easily be accounted for by their failure to notice the less conspicuous disturbances which an intelligent patient will remember.

4. *General Symptoms.* Of great importance are symptoms of a general or indefinite nature, for these frequently lead to the erroneous diagnosis of neurasthenia. Unusual fatigue or exhaustion after physical exertion is the commonest. Less frequent is a sense of mental tire or of depression. Pains of various kinds, neuralgic or muscular, were the first symptoms in a number of patients. Anemia is not a common early symptom, and when progressive, has an ominous significance. I have seen it associated with anorexia, persistent diarrhea, and achylia. With the onset of these symptoms, a blood pressure usually above 220 fell to about 170 mm.

Hemorrhages of one kind or another occurred as an early symptom in nineteen of the deceased and six of the living patients. Of these patients, eight and three respectively had epistaxis. The other forms of hemorrhage were hemoptysis in nine patients, all deceased, and probably dependent upon marked passive congestion of the lungs; gastro-intestinal hemorrhage, hematuria, and uterine hemorrhage, each in a single case. Retinal hemorrhages have not been included in this enumeration, but have been grouped with the ocular manifestations. One patient came to me because he thought a subconjunctival ecchymosis indicated that he had high blood-pressure; he had had no previous warnings. Purpuric manifestations in the skin have not occurred early in any patient of this group.

Gastro-intestinal disturbances were not prominent in the early histories of these patients, and do not appear to me to bear any definite relation to the disease, apart from terminal chronic uremia. Among unusual early symptoms may be mentioned intermittent claudication or sudden giving out of the legs, or senile gangrene, all depending upon arterial narrowing; also tinnitus aurium. Thirst of an intense nature I have discovered occasionally in

association with polyuria, and it has been the indication of a bad outlook. Cough, in many cases depending upon a preëxisting chronic bronchitis, but in some the evidence of chronic passive congestion of the lungs, has in a few cases preceded notable dyspnea.

5. *Symptoms Depending upon Other Diseases.* Diabetes has been the most common antecedent disease in this group of patients. Thirty-three patients (7.2 per cent. of the whole number of 458) have been known to suffer from this for a variable length of time before the onset of any symptoms indicative of cardiovascular or renal disease. In the tabulation of polyuria as an early symptom, all cases of diabetes have been excluded so far as possible. Prostatic or bladder disease was coincident in a number of patients. Retention of urine was the initial symptom in three of the patients, all living, and occurred very early in one of the deceased. Renal colic or the passage of a renal stone occurred in seven of the deceased and four of the living patients at an early period. Chronic bronchitis was an associated or antecedent disease in a considerable group. Where severe, it necessarily introduces an error into the tabulation of dyspnea as a symptom of cardiac insufficiency associated with the hypertensive arterial disease.

VII. Causes of Death and the Relation of Early Symptoms to Them. In my previous paper[1] I tabulated the causes of death and the prominent early symptoms for 100 of the cases here reported. At that time it was impossible to obtain full information for the remainder. Such information with reference to symptoms has now been secured for 212 cases, and with reference to exact causes of death for 184 patients dying prior to June, 1912. These data are shown in Table V. In addition, the number of times that each symptom has appeared as the first or an early symptom among the 246 cases still living on that date is shown for each vertical column. In reading the table, certain facts should be borne in mind. The tabulation is primarily one of symptoms, and several symptoms have usually occurred together in the same patient. The footings of the vertical columns, therefore, represent the number of cases

[1] Janeway, Theodore C. A Study of the Causes of Death in One Hundred Patients with High Blood-pressure, Jour. Amer. Med. Assoc., 1912, lix, 2106.

TABLE V.—The Relation of Prominent Early Symptoms with High Blood-pressure to Causes of Death.

Symptoms.												Death.			
Dyspnea.	Edema of lungs.	Angi-noid pain.	Edema of legs.	Poly-uria.	Visual dis-turb-ance.	Head-ache typi-cal.	Hemi-plegic at-tacks.	Verti-go.	Loss of flesh.	Fatigue, pains.	Albumin and casts, acc. dis-covery.	Causes of death.	Male (% of total known, 137).	Female (% of total known, 47).	Totals	
48	4	11	15	11	2	3	4	2	10	7	4	Gradual cardiac insufficiency	48 (35.0%)	12 (25.5%)	60	32.6% of 184 known deaths
18	1	3	1	29	9	16	7	3	13	10	4	Uremic convulsions coma or gradual uremia	31 (22.6%)	15 (31.9%)	46	40.8% of 184 known deaths
11	0	2	3	1	2	4	5	3	3	7	1	Cerebral apoplexy or its results	20 (14.6%)	9 (19.1%)	29	
3	0	6	2	1	0	1	1	0	0	0	1	Angina pectoris	10 (7.3%)	0	10	
6	3	1	1	2	0	0	0	0	1	2	0	Edema of lungs	6 (4.4%)	1 (2.1%)	7	
2	0	0	0	0	0	1	1	0	0	1	0	Progressive anemia	1 (0.7%)	2 (4.3%)	3	
0	0	0	1	0	0	0	0	0	0	0	0	Pericarditis	1 (0.7%)	0	1	
3	0	3	2	1	0	0	0	0	0	3	1	Complicating acute infectious disease	9 (6.6%)	4 (8.5%)	13	
1	0	1	0	1	0	2	1	1	1	3	0	Other accidental causes	7 (5.1%)	2 (4.3%)	9	
11	3	7	1	5	0	3	5	0	3	3	1	Unknown	25	3	28	
3	0	1	0	1	0	1	0	0	1	1	0	Sudden	4 (2.9%)	2 (4.3%)	6	
106	11	35	26	52	13	31	24	9	32	37	12 (all men)		162	50	212	
(50%)	(5.2%)	(16.5%)	(12.3%)	(25%)	(6.1%)	(15%)	(11.3%)	(4.2%)	(15%)	(18%)	(6%)					
94	3	42	27	45	13	29	10	35	9	59	13 (5 women)					
(38.2%)	(1.2%)	(17%)	(10.9%)	(18.2%)	(5.3%)	(12%)	(4%)	(14.2%)	(4%)	(24%)	(5.3%)					

Percentages of total number deceased, 212.

Symptoms in living patients.

Percentage of total number living, 246.

in which the particular symptom has occurred before the date of my first examination, or definitely at an early period of the illness. Dyspnea on exertion and paroxysmal dyspnea occurred in association so frequently that they have been grouped in a single column, not separated as in my previous study. Only the more prominent symptoms, those occurring with considerable frequency, are here included.

The discussion of the creditability of the diagnosis under the various categories in the early part of this paper should be borne in mind. It should be especially remembered that the deaths credited to uremia presumably contained some cases of apoplexy and that pericarditis undoubtedly occurred much more frequently. Wherever a terminal uremia carried off a patient after a long period of cardiac failure, the death has been credited to cardiac insufficiency, but apoplexy ending the scene has always been considered the immediate cause of death. Also, the endeavor has been made as much as possible to eliminate from the cases dying of edema of the lungs all those with the common, gradual terminal edema, and to include only those with acute suffocative edema of the lungs. It is not probable, however, that this has been entirely successful. The thirteen patients dying of complicating acute infectious disease comprise nine cases of pneumonia. "Other accidental causes" consist of automobile accidents, deaths from surgical operation, drowning, carcinoma, and other wholly unrelated diseases. The six sudden deaths are presumably from angina pectoris or apoplexy.

Discussion of Table V. The results of this tabulation are very similar to those obtained in the study of 100 cases already reported. (See Table II of that paper.) They do not materially alter the conclusions then drawn. They permit, however, of more definite deductions. They may be studied from three points of view: (1) the relative proportion of deaths from the various causes enumerated; (2) the numerical relations of the various symptoms and symptom groups to one another and to the causes of death; and (3) the comparative frequency of the individul symptoms in the patients already deceased and in the group of those still living.

1. *Distribution by Causes of Death.* The type of death was known for 184 of the 212 deceased patients; for 28 it could not be stated exactly. While the largest total number, 60 (32.6 per cent.) died a gradual cardiac death, if one groups together deaths from uremia and from apoplexy in a "cerebral" group, as did Bright, 75 (40.8 per cent.) are thus included. It is particularly interesting to note the almost exact correspondence of this with Bright's tabulation of the causes of death which he traced in 70 of his cases, 30 of them (42.8) dying a cerebral death with apoplexy, coma, or convulsions. Cardiac insufficiency was a conception which did not exist in Bright's day, and it is impossible from his figures to obtain any clear idea of how many of his cases should be classed in this category. If in Table V one considers the deaths from angina pectoris, from edema of the lungs, from pericarditis, and probably some of the sudden deaths as cardiac, then it is evident that the two main groups—the cardiac and the cerebral—are almost equal, over 40 per cent. dying in each of these ways, about 12 per cent. of complicating disease, accident or unrelated causes, while a very small number (1.6 per cent.) ran the course of a progressive wasting disease with severe anemia.

(*a*) *Sex Distribution.* At the right hand of Table V are two columns indicating the total number of men and women dying in each of the groups, and the percentage relations which these numbers bear to the total number of deceased males and females. While variation from the general sex distribution of the whole group in the three larger categories is shown only in the deaths from uremia, this difference is not so great as to be free from the possibility of chance. The two next categories, however, death by angina pectoris and by acute edema of the lungs, show a divergence from the sex distribution of the group so extreme as, I think, to indicate clearly a definite difference in sex predisposition. Not a single woman died in an anginal seizure and only one in an attack of edema of the lungs, as against respectively ten and six men.

(*b*) *Age in Relation to Causes of Death.* A tabulation of the ages by decades of those dying in each group, giving the median or middle point, the mode or the largest number for any decade, as well as the second greatest number is shown in the following table:

TABLE VI.—Ages in Relation to Causes of Death

Causes of death.	Males. Mode.[1]	Males. Median.	Females. Mode.	Females. Median.
Cardiac insufficiency	50 to 59 60 to 69	50 to 59	60 to 69 50 to 59	50 to 59
Uremia (gradual and coma)	40 to 49 50 to 59	50 to 59	60 to 69 40 to 49	50 to 59
Cerebral apoplexy	50 to 59 60 to 69	50 to 59	60 to 69 ?	60 to 69
Angina pectoris	60 to 69 50 to 59	60 to 69	no women	
Acute infectious disease (mostly pneumonia)	50 to 59 70 and over	50 to 59	70 and over no other	70 and over

A comparison of Table VI with Fig. 1 shows that the mode, fifty to fifty-nine in the cardiac and the apoplexy groups for the males, is the same as the mode for the total deceased males. On the other hand, for the females the mode in the cardiac, the uremic, and the apoplexy groups is a decade higher, that is, sixty to sixty-nine, which agrees with the mode for the total number of deceased females as shown in Fig. 1. It will be noted that the mode for the uremic group for the men (40 to 49) is a decade lower than the median for the total group of deceased. But the mode for angina pectoris (all men) is sixty to sixty-nine years, which is higher than the average mode (50 to 59) for the men. As will be seen, the median, or the dividing point, for the men is the fifty to fifty-nine-year group for all the deaths except angina pectoris, where it is a decade higher; while for the women, a median of fifty to fifty-nine years applies only to the cardiac and uremic, being a decade higher for the apoplectic, and still a decade higher (seventy years and over) for those dying of acute infectious diseases.

A study of the second largest groups is of interest as showing tendencies. For the men dying a cardiac death there seems to be a tendency toward a decade higher than the median for that group, and for the women there is a tendency to approach the median. In the second largest group for the uremic men there is a tendency of coincidence with the median, while for the women there is an apparent tendency for death at an earlier age, forty to forty-nine

[1] The two sets of figures for the mode indicate the largest number and the second largest number for each group. The number of patients dying of edema of the lungs, seven in all, is too small to use as a criterion of tendencies.

years. The tendencies for the men dying of apoplexy, as expressed in modes and median, are exactly like those of the men dying a cardiac death.

It seems probable that this table furnishes an indication of the composite nature of the uremic group, made up in part of elderly arteriosclerotics, in part of patients with contracted kidneys, and younger persons with inflammatory kidney lesions.

(*c*) *The Relation of Blood-pressure to Causes of Death.* Table VII shows from various standpoints the relation between the height of the observed blood-pressure and the final cause of death.

TABLE VII.—Height of Blood-pressure in Relation to Cause of Death

	Mode. (Of special group.)	Median.	Per cent. at or below median (220) for whole group.	Per cent. above median (220) for whole group.
Cardiac insufficiency .	215 to 220	210	68.3	31.7
Uremia (gradual and coma)	215 to 220	220	52.1	47.9
Cerebral apoplexy . .	225 to 230	225	41.4	58.6
Angina pectoris . . .	175 to 180	200	80.0	20.0
Edema of lungs . . .	245 to 250	240	28.6	71.4
Acute infectious disease (mostly pneumonia) .	175 to 180	185	84.6	15.4

NOTE.—Of the "sudden" deaths not included in the above there were five in all —four men and one woman. The blood-pressures of the men were: one, 175; two, 210; one, 240 mm.; and the one woman has a pressure of 260.

The figures speak for themselves and require little comment. The differences are so striking as practically to preclude the operation of chance, except in the case of the small group of patients (seven in all) dying of acute edema of the lungs. Both the mode and the median for this group and the number of cases over 220 mm. are the highest noted for any of the groups. It is significant that the two cerebral groups, those dying of uremia and of apoplexy, show a tendency to marked hypertension, the apoplexy cases especially, while the patients dying of gradual cardiac insufficiency have a median of blood-pressure below the median for the entire group, and those dying of angina pectoris a still lower one, the lowest of all being found in the case of patients dying of acute infections. This table would seem to indicate that, other things

being equal, a systolic blood-pressure persistently above 200 mm. constitutes a certain presumption in favor of termination by uremia or apoplexy.

The discussion of factors bearing upon duration of illness, from the first discoverable symptoms to death, involves a number of considerations which must be taken up in relation to the symptoms, and will, therefore, be discussed subsequently.

2. *Distribution by Symptoms.* Table V shows the number of times that each of the more important symptoms has been mentioned in the anamnesis of these patients. Since the vast majority complained of more than a single symptom, it must be clearly understood that the footings of the vertical columns represent only the total number of deceased patients who had at some time during the early part of their indisposition noted the particular symptom tabulated in that column. The totals of the vertical columns must not be added together and compared with the total number of patients. The four columns to the left of the double ruling contain the symptoms referable to the cardiac changes associated with high blood-pressure. The columns to the right contain symptoms referable to the kidneys and the eyes, circulatory and toxic cerebral manifestations, symptoms due to disturbed nutrition, and the indefinite fatigue or pains which are often complained of.

The most striking fact about the table is the frequency of dyspnea as compared with any other symptom. It occurred in exactly half of all the patients. The next most frequent symptom was urinary disturbance, complained of by somewhat less than a quarter of all the patients. It must be remembered that this included cases of urinary disturbance from local causes which could not be separated from the cases with true nephritic polyuria. The number of patients with anginoid pain on exertion (thirty-five in all) will, I think, seem surprisingly large to those whose experience is mainly in hospital wards; and, on the other hand, the thirteen patients with early disturbance of vision will seem few. Both symptoms, I believe, indicate that persistent high blood-pressure in such a group of well-to-do individuals is the evidence of what is predominantly a circulatory rather than a renal disease. This is

again indicated by the early occurrence of hemiplegic attacks in twenty-four of the patients, and of edema of the legs in twenty-six. That thirty-seven of the patients should have sought medical advice largely because of unusual fatigue or of neuralgic or muscular pains suggests the need of great caution in making the diagnosis of neurasthenia in persons past middle life. It should never be made without an instrumental determination of the blood-pressure. In only twelve of the 212 deceased patients was the existence of disease revealed by the discovery of albumin and casts in the urine and in only four by the discovery of high blood-pressure in men who considered themselves in perfect health and who, on cross-examination, could not remember any departure from normal health.

Had the anamnesis not been carefully taken with reference to the existence of symptoms easily overlooked by the patient himself, the number of these accidental discoveries would probably have been greatly increased. They demonstrate the value of systematic examinations in revealing unsuspected disease and suggest the wisdom of an occasional examination of the urine and the blood-pressure in all persons past middle life. A yearly examination by the family physician of all his patients should become the rule. It is certainly as much called for among the elderly as among school children, and is in line with the progress of preventive medicine. But a careful physical examination is not the sole means of detecting disease. It is equally important that the physician should understand the art of history taking and the significance of symptoms.

(*a*) *The Relation of Blood-pressure to Early Symptoms.* The relations of the blood-pressure reading to some of the symptom groups is shown in Table VIII. The main indications which this table afford are that the patients with anginoid pain and with the indefinite neurasthenic symptoms tend to run below the median blood-pressure, while the patients with headache, polyuria, and apoplectic and hemiplegic attacks tend in the opposite direction.

TABLE VIII.—Height of Blood-pressure in Relation to Prominent Early Symptoms.

Symptoms.	Deceased.				Living.			
	Blood-pressures.				Blood-pressures.			
	165 to 220 Per cent.	Over 220 Per cent.	Modes. (For special groups).	Median.	165 to 220 Per cent.	Over 220 Per cent.	Modes. (For special groups).	Median.
Dyspnea	56.6	43.4	235 to 240 185 to 190	220	57.4	42.6	175 to 180 215 to 220	200
Anginoid pain	68.6	31.4	175 to 180	195	78.6	21.4	175 to 180 185 to 190	190
Polyuria	44.2	55.8	215 to 220 225 to 230	230	75.6	24.4	185 to 190	200
Headache, typical	51.6	48.4	215 to 220 225 to 230	220	72.4	27.6	215 to 220 195 to 200	210+
Hemiplegic and apoplectic attacks	47.6	52.4	225 to 230	220+	88.9	11.1	185 to 190	190
Vertigo	44.4	55.6	215 to 220	220+	71.4	28.6	175 to 180	200
Loss of flesh	53.1	46.9	215 to 220	220	88.9	11.1	175 to 180	180+
Neurasthenic symptoms (fatigue and pains)	62.2	37.8	185 to 190 175 to 180	215	83.1	16.9	175 to 180 165 to 170	190+
Albumin and casts, (accidental discovery)	58.3	41.7	215 to 220	220	76.9	23.1	185 to 190	190+

NOTE.—Computations have been made from 220 mm., the median for the group of deceased patients.

(*b*) *The Relation of Early Symptoms to Causes of Death.* A comparison of the frequency of individual symptoms in the different groups arranged by causes of death (Table V) brings out certain prominent clinical types which hypertensive cardiovascular disease assumes. Cardiac symptoms occur three times as frequently in patients who eventually die a cardiac death as in patients who die a uremic death, and five times as often as in those who die of apoplexy. What I have previously designated as "typical" headache, on the other hand, has occurred in sixteen patients who subsequently succumbed to uremia as against three who died a cardiac death, and four who died of apoplexy. Urinary disturbance was more than twice as frequent in the group terminating by uremia and visual disturbances more than four times, notwithstanding the fact that the total number of patients was only three-fourths of the total dying of heart failure. The relation of hemiplegic attacks to the eventual death is less striking, but taken in relation to the totals, it indicates about a double frequency of this symptom in those dying a cerebral death of one or the other form. The relation of anginoid attacks to the probability of death in an anginal seizure is a matter of some interest. Four of the ten patients dying of angina pectoris did not have anginal attacks early in the disease, and of thirty-five patients who complained of definite precordial or substernal pain or oppression on exertion only ten finally died in an anginal paroxysm. Eleven persons with anginoid pain died a gradual cardiac death. However, in the deaths from angina pectoris and acute suffocative edema of the lungs, previous attacks of a similar nature figure in the anamnesis of a high proportion of the patients.

3. *The Relation of Early Symptoms in the Deceased and Living Groups.* The relative frequency of certain of the early symptoms among the deceased as compared with the living (Table V) shows interesting resemblances and still more interesting differences. Dyspnea was a little less frequent among the living; early anginal pain and early edema of the legs were almost identical. Attacks of edema of the lungs, however, were conspicuously less numerous in the living, which rather confirms my belief in their serious prognostic significance. Urinary disturbances and typical head-

ache show about the same relations as the dyspneas in the two groups. The accidental discovery of albumin and casts likewise occurs in the same ratio, but among the living were five women; there were no women with this finding in the deceased group. This indicates perhaps an increasing knowledge of this type of disease among the laity and consequent increase in precautionary visits to a physician. Hemiplegic attacks were much less frequent among the living. The whole question of the significance of apoplectic attacks, however, will be considered by itself later. Vertigo or dizziness, judged by its incidence in the two groups, must be considered a symptom of trivial moment. It seems to be decidedly more common in the elderly arteriosclerotic patients than in those whom one would classify as cases of primary contracted kidney. Visual disturbances show a rather unimportant difference, which it is difficult to explain.

No symptom was more strikingly different in the group of the deceased and the living patients than loss of flesh. From this, I am inclined to the conclusion that this symptom must be looked upon as a serious omen. In order to be quite safe in such a conclusion, however, I restudied the records with reference to the duration of illness in the deceased patients showing this symptom and the time before death when emaciation began. Of the thirty-two deceased patients who showed this symptom early, nineteen died in five years, thirteen in less then four years, eleven lived six years and over from their initial symptom. In these patients, loss of flesh was manifested in three ways. One patient lost a moderate amount of weight at the start of her illness, some of which was regained subsequently. She died five and one-half years later. Six patients exhibited a slow and steady decline in weight of only moderate extent, over periods varying between five and eleven years. These two types of loss in weight are evidently without serious import. Seven patients, however, showed progressive and marked loss of flesh, three dying in less than one and one-half years, and in two and one-half years, and the remaining three in from three to three and one-third years after emaciation set in. It seems to me conclusive from this finding that rapid, continued loss of flesh must be considered as pointing toward a fatal termi-

nation in less than the average time for patients with high blood-pressure.

Fatigue and pains, on the other hand, showed a relation to an earlier stage or a milder type of disease, by occurring almost twice as frequently in the patients still living.

VIII. Additional Data from Histories and Physical Examination. 1. *Apoplectic Attacks.* An attempt was made to discover the total number of deceased patients in whom apoplectic or hemiplegic attacks, or their analogues, occurred at any time in the course of the disease. They were mentioned by fifty-eight patients in all, forty-three men and fifteen women. These are respectively 21.1 per cent. of the total males and 31.2 per cent. of the total females whose type of death is known. The sex incidence of apoplexy as a cause of death or of hemiplegic attacks during life is not materially different in the two sexes.

2. *Anginal Attacks.* I have been especially interested in the frequency of anginoid pain among these patients. Of the deceased, thirty-two, or 19.6 per cent., of all males, and six women, or 12.2 per cent. of all females, had this symptom in some degree. Among the living, however, it is surprising to find that twenty, or 19.6 per cent., of all the women complained of anginoid pain as against twenty-six men, or 18 per cent. of all the males. When one compares this with the deaths from angina pectoris, all ten of which were in men, the only reasonable explanation would seem to be that the milder anginoid attacks are commoner in women than in men, and that when they occur, women avoid sudden and forced exertion and excitement far better than men; for this reason, for the most part they escape death in an anginal paroxysm. In the rest, it is probable that syphilitic aortitis is commoner among men than among women and is the cause of some of the anginal deaths.

3. *Cardiac Arrhythmias.* My record of the existence of arrhythmia among these patients depends either upon my detection of it at the time of examination, upon the definite knowledge of it obtained from the patient's physician, or a definitely satisfactory description of the arrhythmia by the patient himself. My data are, therefore, defective, and greatly underestimate the total

frequency of arrhythmia which would have been found had these patients been followed throughout a period of years. Of the 212 deceased patients, seventy-one had some degree of cardiac insufficiency at the time of examination. Only 8 patients had the perpetually irregular pulse indicative of auricular fibrillation. It is noteworthy to record that six of these eight patients were treated with digitalis and the results were known: the result was satisfactory in four, slight in one, and without benefit in the other. Contrasted with this were six cases with failing hearts and regular rhythm, of whom four responded well to digitalis, two brilliantly. The relief of dyspnea was especially notable as Miller[1] reported last year. Of the other arrhythmias, extrasystoles were noted in nine patients, paroxysmal tachycardia in three, heart-block in one, and an unspecified arrhythmia in one. Eight of the patients complained of serious palpitation. Among the 246 living patients, only twenty-five had insufficient hearts when examined. Only two patients had the evidence of auricular fibrillation; seventeen patients had extrasystoles, four paroxysmal tachycardia, one heart-block, one a marked sinus arrhythmia, and one an unspecified irregularity.

I have been somewhat impressed with the less frequent occurrence of fibrillation of the auricles in the insufficient heart, secondary to high blood-pressure, as contrasted with valvular disease. My evidence for this is not altogether satisfactory, as it rests in part on the incomplete figures just given. A study of the records of seventy-five patients with auricular fibrillation, electrocardiographically recorded by Dr. Stuart Hart at the Presbyterian Hospital, showed that fourteen had a blood-pressure above 180 mm.; this is only one-fifth. This figure could only have absolute value if it were known what proportion of the cases of cardiac insufficiency at the hospital were due to hypertensive disease and what proportion to valvular disease during the same period. This I have been unable to calculate.

4. *Evidence of Cardiac Hypertrophy.* My records contain statements as to the existence of evidence of cardiac hypertrophy and its degree in 193 of the deceased patients and 244 of the living.

[1] Miller, J. L. Trans. Assoc. Amer. Phys., 1912, xxvii, 137.

What I have considered such evidence has been enlargement of the percussion area, displacement of the apex-beat downward and to the left, or a definite lifting character of the impulse, singly or combined. No radiographic studies have been made. The accentuated aortic second sound has not been considered such evidence, but has been tabulated separately. My records show the following:

TABLE IX.—Evidence of Cardiac Hypertrophy in Four Hundred and Thirty-seven Patients.

	Deceased.[1]	Living.
None	8	39
Questionable	4	5
Slight	41	98
Moderate	96	83
Marked	44	19
	193	244

This table, of course, does not indicate the existence or non-existence of cardiac hypertrophy, but only my ability to detect it. It is interesting especially as an indication of the very considerable number of patients in whom even a careful physical examination will fail to show an hypertrophied heart, and that only the sphygmomanometer makes the diagnosis of this type of cardiovascular disease definite. The tabulation is particularly valuable, therefore, as indicating the importance of instrumental blood-pressure observations in diagnosis. Of further interest is the difference between the two groups of patients. Not only was proof of cardiac hypertrophy lacking in nearly five times as many of the living as the dead, but the slighter grades of hypertrophy were numerically more frequent and the marked grades much less. It is altogether probable, therefore, that the group of the living is made up of individuals at an earlier stage of the cardiovascular disease.

5. *Accentuation of the Aortic Second Sound.* A definite note as to the character of the aortic second sound was made on 163 of the deceased and 226 of the living patients. My findings are shown in the table which follows:

[1] For 19 of the deceased patients the data as to existence or non-existence of hypertrophy were not recorded.

TABLE X.—Incidence of Accentuation of Aortic Second Sound in Three Hundred and Eighty-nine Patients

	Deceased.	Living.
None	38	67
Questionable	1	1
Slight	21	55
Moderate	75	88
Marked	28	15
	163	226

It will be seen that no accentuation of the aortic second sound could be heard in a considerable proportion of the cases, in thirty-eight (23.3 per cent. of the 163 deceased for whom this information was recorded), and sixty-seven (29.6 per cent.) of the living. This information is within the limits of the personal equation of the examiner, absolute, not merely relative, as are the data regarding cardiac hypertrophy. The causes for absence of accentuation of the aortic second sound in hypertension are various; emphysema of the lungs, marked obesity, senile rigidity of the thorax, and other unknown conditions modify the transmission of vibrations. Beyond these, it seems to me clear that there are conditions within the heart and aorta in these patients which modify the intensity and pitch of the aortic second sound in addition to the aortic blood-pressure. For instance, over the dilated aorta of syphilitic aortitis an extremely loud, ringing sound may be heard when the blood-pressure is normal. In this connection I wish to emphasize again the fact that without instrumental blood-pressure determinations, many cases of hypertension must inevitably be overlooked, even by the most expert examiner, as in many of these patients neither an hypertrophied heart, nor an accentuated second sound, nor a pulse which impresses the examiner as tense, will be found. So far as the further evidence of the table goes, very marked accentuation of the aortic second sound was proportionately more than twice as frequent in the deceased than in the living groups, and moderate accentuation was about equal, the slighter degrees greatly preponderating in the living. This shows a rough correspondence with the median for the blood-pressures of the two groups, as would be expected.

6. *Evidence of Arteriosclerosis of the Peripheral Arteries.* The histories studied include definite statements as to the condition of the larger peripheral arteries in 171 of the deceased and 231 of the living patients. My findings are shown in Table XI.

TABLE XI.—Evidence of Arteriosclerosis in Four Hundred and Two Patients

	Deceased.	Living.
None	65	117
Questionable	1	0
Slight	14	46
Moderate	60	55
Marked	31	13
	171	231

Of particular note in this table is the large number of patients in each group in whom the radial, brachial, and temporal arteries were free from evident thickening, elongation, or calcification. It demonstrates how independent permanent high blood-pressure is of arteriosclerosis in the ordinary sense, that is, arteriosclerosis of the larger accessible peripheral vessels. It is the reverse side of the well-known fact that extensive arteriosclerosis of these vessels is frequently found associated with blood-pressure not above the normal. The slight degrees of arterial thickening are especially evident among the patients still living and the marked among those that have died. The evidence here, as for cardiac hypertrophy, is therefore, in the main, that arteriosclerosis of the larger peripheral vessels should be looked upon as a secondary lesion similar to the cardiac hypertrophy. This is further brought out by an examination of the eventual causes of death in those patients who showed moderate or marked degrees of arteriosclerosis. By "slight" arteriosclerosis in the preceding tabulation I have meant arteries which were just distinctly palpable when empty, or showed slight tortuosity. This is so regular a finding in individuals past middle life that it does not seem to me to have any strict relation to the disease here studied. The considerable degrees of arteriosclerosis, however, are evidence of more than mere wear and tear. A tabulation of all the cases showing more than the slighter grades is shown in Table XII.

TABLE XII.—The Relation of Moderate or Marked Arteriosclerosis to Causes of Death in Ninety-one Deceased Patients

Causes of death.	Moderate.	Marked.	Totals.
Gradual cardiac insufficiency	13	6	19
Uremia	18	13	31
Cerebral apoplexy	10	3	13
Angina pectoris	1	0	1
Edema of the lungs	2	3	5
Acute infectious disease	1	1	2
Other causes, unrelated, etc.	10	2	12
Unknown	5	3	8
	60	31	91

To my great surprise the above table shows a marked preponderance of disease of the large peripheral arteries among the patients dying of uremia. I had expected that the group dying of insufficient hearts would contain the bulk of the arteriosclerotics. My general impression was that arteriosclerosis was associated with sclerotic changes in the coronaries and consecutive myocardial, nutritional disturbances, leading to myocardial insufficiency. The examination of these histories has shown, however, that these striking degrees of arterial thickening and elongation frequently occur in young persons with the picture of so-called primary contracted kidney or other primary renal disease. Some of these patients have been under forty years of age. But again, a large number of the patients with anginoid pain and presumptive coronary sclerosis have been free from any traces of peripheral arterial thickening. This emphasizes what is beginning to be more generally appreciated—that the distribution of arteriosclerotic lesions is most variable; that extensive cerebral or coronary arterial disease may exist without any evidence of thickening of the accessible arteries of the extremities; that certain causes for arterial disease, the *treponema pallidum,* for instance, have a strict elective affinity for limited portions of the arterial system—all facts tending to suggest that the arterial system cannot be looked upon as a whole in the development of its pathological processes, but that local differences in susceptibility to disease exist, and that local causes play a considerable part in the distribution of its lesions.

Further, this table strengthens the argument drawn from the preceding table (Table XI) that peripheral arteriosclerosis in

hypertensive disease must be looked upon usually as result, not cause. This view seems to be taken by Jores[1] and has been a common one among clinicians. It also fits well with Marchand's[2] studies in arteriosclerosis, which go to show that cardiac hypertrophy is not, as a rule, associated. For this reason it seems to me that to speak of the type of disease under discussion as arteriosclerosis, or hardening of the arteries, as is so frequently done, is altogether erroneous and productive of false views of the causation of high blood-pressure.

7. *Urinary Findings.* (*a*) *Albumin and Casts in the Urine.* In the majority of cases careful urinary examinations were made at the time of my physical examination. Only the analyses made in my own laboratory or in that of my father have been considered in studying the significance of these urinary findings. The significance of this information is wholly diagnostic. I have no data from which any statement can be made as to incidence of albuminuria and cylindruria during the course of hypertensive cardiovascular disease. It was of interest from the standpoint of the usefulness of a single urine analysis, as a means of diagnosis of this type of disease, to tabulate my findings.

Of the 212 deceased patients, twenty-one showed neither albumin nor casts in the urine when examined; and of the 246 patients still living, ninety-five had urines negative in both these respects. In twenty-three of the deceased and nineteen of the living, albumin was found without casts; in only two and one case respectively in any considerable amount. In seventeen of the deceased and in thirty-two of the living, casts were discovered in urine which did not show albumin by the nitric-acid-ring test; again, in only one and two patients respectively were they numerous.

Of the deceased patients, 114 out of the 182 of whom I have definite information in this respect, or 62.6 per cent., had definite amounts of albumin and casts; of the living, eighty-five out of 236 of whom I have records, or 36 per cent., showed both albumin and casts. In twenty-five of the former and forty-two of the latter

[1] Jores. Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie vom patho- logisch-anatomischen Standpunkt. Verhandl, deutsch. path. Gesellsch., 1908, xii, 187.

[2] Marchand. Verhandl. d. Cong. f. inn. Med., 1904, xxi, 60.

there were but few casts and a trace of albumin. In the remainder eighty-nine (48.9 per cent.) of the deceased and forty-two (17.8 per cent.) of the living, albuminuria was moderate or marked; and casts, except in a few cases, were numerous. No study as to types of casts has been made. Information on this point which is beginning to come from the life insurance companies in such studies as those of Barringer[1] will have much more positive prognostic value.

A tabulation of those cases showing more than a trace of albumin with casts, in whom the causes of death were known, follows:

TABLE XIII.—Relation of Moderate or Marked Albuminuria with Casts to Causes of Death in Seventy-nine Patients.

Causes of death.	Number.
Gradual cardiac insufficiency	24
Uremia	30
Cerebral apoplexy	8
Angina pectoris	3
Edema of the lungs	3
Progressive anemia	2
Pericarditis	1
Other accidental causes	5
Sudden	3
	79

It is clear that a negative urine examination has the very slightest value in excluding the existence of cardiorenal disease of the type presented by these patients. This, of course, is well known, but cannot too often be insisted on. These urinary studies also bring out the mixed character of the material investigated. Large amounts of albumin and large numbers of casts belong especially with the true chronic inflammatory lesions of the kidney. They are also to be expected during periods of marked cardiac insufficiency. For this reason, the deceased group showed their presence much more frequently than the living group.

(*b*) *Specific Gravity of the Urine.* Twenty-four-hour urine specimens were not obtained from the majority of the persons studied. The urine specimens examined, however, were always mixed specimens from afternoon, night, and morning, representing about sixteen hours out of the twenty-four. The records of specific

[1] Barringer, T. B. The Prognosis of Albuminuria with or without Casts, Arch. of Int. Med., 1912, ix, 657.

gravity obtained in such specimens have only a relative value, and they are introduced here without a desire to draw more than very guarded conclusions.

TABLE XIV.—Specific Gravity of Urines, Deceased and Living

	Deceased.	Living.
Normal, 1.015 to 1.022	68	135
Low, below 1.015	78	43
High, above 1.022	25	50

TABLE XV.—Specific Gravity of Urines in Relation to Causes of Death[1]

	Urines.				
Causes of death.	Normal.	Low.	High.	Unknown.	Total cases
Cardiac insufficiency	23	24	4	9	60
Uremia	13	24	5	4	46
Apoplexy	10	9	5	5	29
Angina pectoris	5	3	2	0	10
Edema of the lungs	3	1	2	1	7
Acute infectious disease	5	1	4	3	13

Two things stand out prominently in these tabulations: (1) the double frequency of low specific gravity in the whole deceased group as against the whole living group; (2) that low specific gravity was found more frequently than normal or high specific gravity definitely only in those patients dying of uremia. In those dying a cardiac death, about an equal number showed a low as a normal specific gravity; in those dying of apoplexy and from intercurrent infections, the greater number had urines of normal or increased specific gravity. The relation, therefore, is manifest between a low specific gravity and the type of disease in which symptoms of renal insufficiency were prominent. On the other hand, low specific gravity urine occurred with such numerical frequency in individual cases of the other types as to have only relative value in prognosis.

8. *The Relationship of Diabetes to High Blood-pressure.* The 458 cases studied contain thirty-six (7.9 per cent.) diabetics. In all but three of these patients, as already mentioned, the diabetes was recognized before the high blood-pressure or before symptoms clearly referable to it were discovered. This number is probably well above what it might be with a different selec-

[1] The patients dying of progressive anemia, pericarditis, unknown, and sudden deaths are not included.

tion of material, for my practice has included a rather unusual number of cases of diabetes. The proportion, however, is obviously too large to be explained by mere chance. The effect of diabetes upon blood-pressure has been the subject of some discussion. Potain[1] included diabetes with chronic nephritis as one of the causes of extreme hypertension. My view[2] has always been that the effect is altogether indirect, the result of the well-known frequency of arterial disease in elderly diabetics. The relation here may well be a double one—primary arterial changes in the pancreas producing the diabetes, or the diabetes leading to widespread arteriosclerosis. Certainly, pure diabetes in young persons, leading to death by coma, never is associated with high, but usually with low blood-pressures. My views have been substantiated by Elliott's studies.[3]

IX. Data Bearing on Duration of Disease. In dealing with conditions of such insidious onset, in which the lesions without doubt long antedate the development of symptoms, it is manifestly impossible to arrive at an exact estimate of the possible or even usual duration. I have endeavored in each case to collate from my records the facts bearing on duration. These facts are: (1) the length of time before death during which any symptoms reasonably attributable to cardiovascular or renal disease existed, calculated to the date of death in the case of the deceased and to June 1, 1912, in the case of the living; (2) the duration of life after high blood-pressure was detected by me, or in the case of the living, the time which had elapsed between my findings of hypertension and June 1, 1912.

1. *Duration of Life from First Symptom.* The first set of facts is shown in graphic form in Charts V and VI, which include complete information on this point obtained from 187 deceased and 244 living patients. The character of the curves for the living and the deceased is strikingly similar. It is probable that a suffi-

[1] Potain. La pression arterielle de l'homme à l'état normal et pathologique, Paris, 1902.

[2] Janeway, Theodore C. The Clinical Study of Blood-pressure, New York, 1904, p. 236.

[3] Elliot, A. The Clinical Study of Blood-pressure Variation in Diabetes and Their Bearing on the Cardiac Complications, Jour. Amer. Med. Assoc., 1907, xlix, 27.

ciently large number of patients would obliterate the lesser irregularities. The median, also, is identical—four years for men and five years for women, in both the deceased and the living groups. The high point of the tabulation for the deceased is reached at one year, while for the living a second apex is found at three years. Whether this is more than accidental, I cannot tell. Cases dying in less than one year from the first development of symptoms

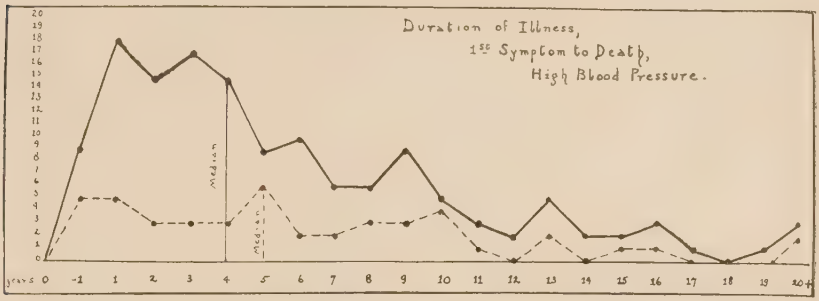
Duration of Illness,
1st Symptom to Death,
High Blood Pressure.
Median
Median
years 0 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20+

CHART V.—Duration of illness, first symptom to death, high blood-pressure; solid line, males, 141; broken line, females, 46; total, 187.

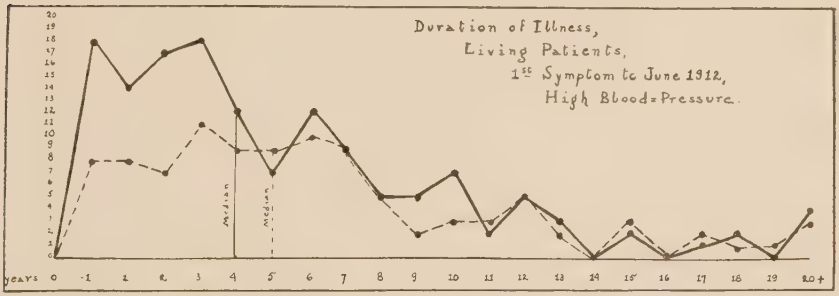
Duration of Illness,
Living Patients,
1st Symptom to June 1912,
High Blood-Pressure.
Median
Median
years 0 -1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20+

CHART VI.—Duration of illness, living patients, first symptom to June, 1912, high blood-pressure; solid line, males, 143; broken line, females, 101; total, 244.

represent to a much larger extent than the others, patients seen in their terminal illness, who were not in a position to give accurate data as to early and minor symptoms. The patients still living represent to a much larger extent those seen in office practice and from whom much more complete information could be obtained. It is probable that this is the real explanation of the early high point for the males in Chart V. This much is clear, that from the

time of the development of symptoms indicative of cardiovascular or renal disease, four years will witness the death of half of the men and five years half of the women. By the tenth year, half of the remainder will also have died, leaving both for the men and the women a quarter of the whole group whose duration of life is ten years or over. These patients diverge from one another so widely in the length of life as to warrant entirely separate consideration. The cases of unusual duration have been subjected to special study. They are shown in abstract form in Table XVI.

TABLE XVI.—Protocol of Thirty-seven Deceased Patients Living Ten Years and Over from Onset of First Symptom.

		Males.	Age	Duration	
Case No.	First symptom.	Prominent early symptoms.	at death.	(years).	Death.
4	Polyuria	Anginoid pain, polyuria, visual disturbance, loss of flesh	70	11	Uremia
14	Diabetes	Gastro-intestinal hemorrhage	63	15	Cardiac insufficiency
17	Accidental discovery, albumin and casts	None	53	19	Cardiac insufficiency
19	Anginoid pain	Anginoid pain	58	11	Angina pectoris
26	Palpitation	Paroxysmal dyspnea, albumin, and casts	52	13	Unknown
44	Headache, typical	Headache, typical; loss of flesh, hemiplegic attack, vertigo, polyuria	46	12	Uremia
48	Dyspnea on exertion	Retention of urine	70	16	Unknown
67	Anginoid pain	Anginoid pain, dyspnea on exertion, paroxysmal dyspnea, odema of legs	58	13	Cardiac insufficiency
81	Fatigue	Dyspnea on exertion, slight	72	10	Apoplexy
86	Accidental discovery, albumin and casts	Anginoid pain +	52	22	Angina pectoris
97	Renal colic	Mental fatigue, headache typical, palpitation, neuralgic pain	54	16	Sudden
109	Polyuria	None	74	13	Pneumonia
121	Palpitation	Paroxysmal tachycardia	62	32	Auto accident
129	Albumin, casts, etc.	Albumin, casts, legs giving out, vertigo, loss of flesh	61	12	Apoplexy
135	Oliguria	Dyspnea on exertion, slight	80	15	Cardiac insufficiency
164	Neuralgic pains	Diabetes	63	10	Pneumonia
165	Diabetes	Anginoid pain	60	10	Angina pectoris

Case No.	First symptom.	Prominent early symptoms.	Age at death.	Duration (years).	Death.
		Males.			
172	Accidental discovery, albumin and casts	Neuralgic pains, albumin, and casts	40	13	Cardiac insufficiency
175	Diabetes	Diabetes, dyspnea on exertion	73	29	Pneumonia
176	Palpitation	Palpitation, vertigo, dyspnea on exertion slight	59	16	Cardiac insufficiency
182	Diabetes, edema of nephritic type, anginoid pain	Anginoid pain	62	14	Cardiac insufficiency
183	Albumin and casts, paroxysmal dyspnea	Albumin and casts, paroxysmal dyspnea, hemoptysis, dyspnea on exertion, loss of flesh, cough	65	14	Cardiac insufficiency
197	Paroxysmal dyspnea	Paroxysmal dyspnea, dyspnea on exertion, polyuria	68	10	Cardiac insufficiency
211	Mild arteriosclerosis	Cough, vertigo, headache, hemiplegic attack	67	17	Drowned
212	Palpitation	Palpitation, dyspnea on exertion	72	13	Apoplexy
213	Diabetes	Edema of legs, anginoid pain	59	11	Pneumonia
217	Edema of legs	Paroxysmal tachycardia, pericardial effusion	59	10	Pericardial effusion
		Females.			
25	Albumin, casts (pregnancy)	Loss of flesh, fatigue	47	23	Uremia
53	Diabetes, renal colic	Loss of flesh, albumin, and casts	61	13	Unknown
63	Diabetes, albumin, and casts	Neuralgic pains, albumin, casts, dyspnea on exertion, paroxysmal dyspnea, visual disturbance	62	10	Uremia
65	Dyspnea on exertion	Dyspnea on exertion, polyuria, edema of lungs, palpitation	56	10	Cardiac insufficiency
75	Hematuria	Hematuria, oliguria, headache typical, gastrointestinal hemorrhage marked, gangrene of extremity, anemia	19	10	Progressive anemia
96	Marked gastrointestinal disturbance, drowsiness	Polyuria, albumin, and casts	44	13	Uremia
103	Edema of legs	Dyspnea on exertion, paroxysmal dyspnea.	64	15	Apoplexy
148	Goitre	Goitre	55	16	Cardiac insufficiency
178	Edema of legs	Anginoid pain, paroxysmal dyspnea	78	30	Pneumonia
187	True psychosis	True psychosis, albumin and casts, general edema, uremia	60	11	Apoplexy

While it is impossible to discuss all the interesting features here presented, certain facts are noteworthy. Seven of the thirty-seven patients were elderly diabetics. In five of the seven, the first symptom was glycosuria or some symptom referable to the diabetes, and it was impossible to distinguish at what period of their diabetes the arterial hypertension supervened. In two, cardiac or renal symptoms occurred at the onset (cases Nos. 103 and 182). Case 182, a man, had general edema for fourteen years before death and anginoid pain early in his disease; he died at the age of sixty-two, of an insufficient heart, and four years before death the blood-pressure was 170 mm. Case 103, a woman, had edema of the legs fifteen years before her demise. She had dyspnea, both on exertion and paroxysmal, many years before death, which followed at the age of sixty-four from apoplexy; her blood-pressure one year before death was 230 mm. systolic and 130 diastolic.

One of the most interesting patients (No. 211) was a man who at the age of fifty developed mild intermittent claudication. He subsequently suffered from neuralgic pains, vertigo, headaches, and had an attack of left-sided numbness. A blood-pressure reading taken five years before death was 185 systolic, 100 diastolic. He was drowned in the Titanic disaster at the age of sixty-seven, with considerable expectancy of life before him.

In three cases (Nos. 17, 86, and 172) the first symptom was accidental discovery of albumin and casts. The duration of life thereafter was respectively nineteen, twenty-two, and thirteen years.

A very striking case was No. 75, a girl who had an acute nephritis following diphtheria at the age of nine. Her clinical course was characterized by a striking hemorrhagic tendency, recurring hematuria with fever, uterine and retinal hemorrhages, consecutive anemia, oliguria, with headache and vomiting, and who after ten years died of anemia consecutive to her losses of blood. Her blood-pressure at the age of nineteen was 210 mm. systolic and 110 diastolic. There was an associated endocarditis in her case.

Case No. 178, a woman, who died at the age of seventy-eight, had edema of the legs thirty years before her death, suffered from anginal attacks and paroxysms of dyspnea for eight years, had

a very moderate hypertension, 170 systolic and 110 diastolic, extensive arteriosclerosis, and finally died of lobar pneumonia.

Somewhat similar cases are Nos. 81, 135, and 212, men in whom the primary disease was clearly senile arteriosclerosis. In contrast to them, case No. 44, a man dying at forty-six, of uremia, had his first headaches twelve years before death. He suffered from headaches, loss of flesh, transient hemiplegic attacks, dyspnea, and polyuria. His blood-pressure was 255 systolic and 170 diastolic two years before death, and he died of chronic uremia. His brother (case No. 41, not shown in the above table) had an almost identical course of eight years, dying at the age of thirty-seven also of chronic uremia. In these two men, headache of the kind I have described of the most intense character was wholly unrelieved by any methods of treatment.

Cases 19 and 67 are noteworthy as illustrating the occasional long tolerance of anginoid pain. In each of these men, this was the first and throughout the prominent symptom, yet the former lived eleven years, dying finally of an anginal seizure, and the latter succumbed to gradual cardiac insufficiency only after thirteen years.

Duration of Illness in Relation to Causes of Death. The duration of illness from the first symptom to death is shown arranged by causes of death in Table XVII.

TABLE XVII.—The Relation of Duration of Illness (First symptom to Death) to Causes of Death

	Duration (years)										
	Under						6 and over				Median
Causes of death	1	1	2	3	4	5	Per cent.		Unknown.	Total.	year.
Cardiac insufficiency	9	3	10	5	5	4	19	(34.5)	5	60	4
Uremia	3	8	6	10	4	4	11	(23.9)	0	46	3
Apoplexy	2	1	4	4	4	6	7	(25.0)	1	29	4
Angina pectoris	0	1	0	2	3	1	3	(30.0)	0	10	4
Edema of the lungs	0	0	3	1	1	2	0	..	0	7	3
Acute infectious disease	2	1	0	2	1	0	6	(50.0)	1	13	5
Progressive anemia	0	0	0	1	0	0	2	(66.6)	0	3	
Pericarditis	0	0	0	0	0	0	1	(100.0)	0	1	
Accidental causes	0	1	1	2	1	1	3	(33.3)	0	9	
Sudden	0	1	1	0	2	1	1	(16.6)	0	6	4
										186	

NOTE.—The percentages of the column, six years and over, have been computed on the basis of the cases where the death was known, eliminating the unknown.

The differences here are not very great between the groups. But, judged either by the median for duration or the number of cases living six years and over, the group dying with uremic symptoms seems to be somewhat shorter-lived; 75 per cent. of these patients died before the sixth year. There were too few persons dying of edema of the lungs to make it safe to draw any conclusions, but it is interesting that the whole seven died before the sixth year of illness. The distinctly greater duration in the case of patients dying of acute infectious diseases is of still more significance when one considers that such intercurrent infection must be looked upon as an accident terminating the underlying chronic disease before it would in itself have led to a fatal issue. It seems fair to conclude, then, that these patients exhibited a less progressive type of cardiovascular disease than the others. I think it is also of some interest to observe that the duration of life in patients dying of angina pectoris was not materially different from patients dying of gradual cardiac insufficiency; in each case, at least 30 per cent. lived for six years and over from the onset of the first symptom.

In the case of the patients living June, 1912, Tables XVIII, XIX, and XX show the first and early symptoms.

It is evident that in a considerable number of instances, the first symptom was one of a minor nature—palpitation, vertigo, or pains, or a preceding disease, such as diabetes. There were, however, six patients who had dyspnea, six who had anginoid pain, one who had edema of the legs, one with general anasarca, one a hemiplegic attack, and one an attack of coma more than ten years ago and who were still living June, 1912. In six, the discovery of their condition was purely accidental. The most significant point in the tabulation of these blood-pressures (Table XXI) is that the median for this group of long duration is exactly the median for the entire living group, that is, 200 mm. This, again, indicates that the exact height of the blood-pressure has very little prognostic value. Of course, it must be remembered that these blood-pressure readings are not in all cases the pressures of ten years ago. The study of these patients suggests the need for extreme reserve in making any prognosis as to the probable duration of life in this type of chronic disease.

TABLE XVIII.—Early Symptoms of Fifty-one Patients (28 Males and 23 Females) Living June 1, 1912, More than Ten Years from Onset of First Symptom

Symptoms.	Total No. of patients.	As a first symptoms in.
Dyspnea (on exertion and paroxysmal)	20	6
Anginoid pain	16	6
Edema of lungs	2	0
Palpitation	13	8
Edema of the legs	8	1
General edema	1	1
Polyuria	6	2
Retention of urine	2	2
Headache[1]	12	1
Vertigo	9	3
Hemiplegic attacks	5	1
Transient coma	1	1
Uremic convulsion	1	0
Drowsiness	1	0
Visual disturbances	1	0
Pains (mainly neuralgic)	8	3
Fatigue (physical and mental)	6	1
Hemorrhages	3	0
Loss of flesh	2	0
Gangrene of extremities	1	1
Intermittent claudication	4	1
Cough	1	0
Diabetes	10	6
Albumin and casts (accidental discovery)	3	3
Cardiac disturbance (accidental discovery)	2	2
High blood-pressure (accidental discovery)	1	1

TABLE XIX.—Ages of Fifty-one Living Patients (28 Males and 23 Females), with Symptoms More than Ten Years from Onset

30 to 39 years	3
40 to 49 years	4
50 to 59 years	15
60 to 69 years	17
70 to 79 years	9
80 and over	3
	51

TABLE XX.—Duration of Illness, First Symptom to June 1, 1912, of Fifty-one Patients Living for Ten Years and Longer from Onset of First Symptom

Years.	Number.
10	12
11	6
12	9
13	5
14	0
15	5
over 15	14
	51

[1] Of these cases of headache, three were typical, nine atypical; the case where headache was the first symptom was of the atypical type.

TABLE XXI.—Blood-pressures of Fifty-one Patients Living More than Ten Years from Onset of First Symptom

Systolic blood-pressure (millimeters).	No. of patients.
165 to 170	4
175 to 180	5
185 to 190	10
195 to 200	6 (median)
205 to 210	8
215 to 220	7
225 to 230	1
235 to 240	3
245 to 250	3
255 to 260	1
265 to 270	2
275 to 280	1
	51

2. *Duration of Life after Finding High Blood-pressure.* The duration of life after my discovery of high blood-pressure in the deceased patients and in those still living is shown in Table XXII.

TABLE XXII.—Duration of Life after Finding High Blood-pressure, Four Hundred and Thirty-eight Patients

	Deceased (to death).		Living (to June, 1912).		
Dying in	Males, per cent.	Females, per cent.	Living after examination.	Males, per cent.	Females, per cent.
Less than 1 year	73 (49.0)	27 (55.1)		51 (37.0)	38 (37.3)
1 year and over	32 (21.5)	10 (20.4)		13 (9.4)	12 (11.8)
2 years and over	14 (9.4)	2 (4.1)		13 (9.4)	10 (9.8)
3 years and over	12 (8.0)	4 (8.2)		18 (13.1)	8 (7.8)
4 years and over	10 (6.7)	4 (8.2)		19 (13.8)	12 (11.8)
5 years and over	4 (2.7)	1 (2.0)		10 (7.2)	9 (8.8)
6 years and over	4 (2.7)	1 (2.0)		14 (10.1)	13 (12.7)
	149 (100.0)	49 (100.0)		138 (100.0)	102 (100.0)

Since my accurate readings date back but ten years, these figures are only useful as suggesting future possibilities. All but 2.7 per cent. of the men and 2 per cent. of the women died within five years of my discovery of hypertension. The few living from six to ten years later, however, show that the duration of hypertensive cardiovascular disease may easily exceed ten years. Absolute information on this point will eventually be afforded by the large life insurance companies. An excellent start has been made in this direction by such work as that of Fisher.[1]

[1] Fisher. The Diagnostic Value of the Use of the Sphygmomanometer in Examinations for Life Insurance, Meeting of Association of Life Insurance Medical Directors, New York, October 4, 1911.

X. Etiology. When this work was undertaken I had hoped that it might also be possible to correlate information of value as to possible etiological factors contributing to the development of arterial hypertension. The range of such factors as were found in the life histories of these individuals was so great as to demand an extensive critical study to yield anything more than the usual text-book catalogue of all the diseases and vices of the human race as the causes of any disease the origin of which is obscure. This attempt was, therefore, abandoned for the time being, in order to devote more attention to the foregoing facts bearing on the clinical features and the prognosis of the morbid state, which, while less important than a knowledge of its cause, seems also less likely to mislead. A similar discussion of the etiology seemed likely to provoke the criticism made by Artemus Ward that "it is better not to know so many things than to know so many things that ain't so."

XI. General Considerations. The question may well be asked whether there is any warrant for bringing together, as I have done, cases of such a diverse nature, which had in common only the single symptom, high blood-pressure. Throughout the preceding pages I have purposely refrained from indicating the clinical diagnosis in these cases. I have done this because the clinical diagnoses which I made ten years ago are not the clinical diagnoses which I would make in these same patients today, and I trust they are not the diagnoses under which such cases will be tabulated ten or twenty years hence. I have endeavored to limit myself to a statement of facts and obvious numerical relationships. Neither the clinical studies of nearly a century nor the experimental investigations of nearly half a century have succeeded in elucidating the real cause of high blood-pressure, nor have the anatomical researches of pathologists resulted in any unanimity of opinion about the relationship of the underlying lesions to one another and to the disease picture. One physician would make the diagnosis of chronic intestinal nephritis in the bulk of these patients, another of arteriosclerosis, a third would take the purely symptomatic point of view and speak of many of them as cases of arterial hypertension. But the latter cannot be a finally satisfactory con-

cept. The adrenalinemia theory, which was so much in vogue of late, is as I have endeavored to show elsewhere,[1] without foundation as yet. It is evident that a large proportion of these patients show at autopsy one or another type of kidney disease, most commonly either the so-called primary contracted kidney, or arteriosclerotic atrophy. In some, however, and I have recently had brilliant examples of this, the kidney lesions are of the most insignificant character, but widespread arteriolar disease exists elsewhere. The tendency is strong for pathologists to return to the original view of Gull and Sutton[2] that this type of disease is primarily a disease of the small bloodvessels.

The character of the lesions has been well described by Jores.[3] The question remains open, however, whether the high blood-pressure precedes or causes the lesion. That the arterial narrowing will heighten a preëxisting high blood-pressure and render it more permanent does not make it clear that the arterial lesion comes first. That arteriosclerosis of the larger arteries may at times extend toward the periphery and produce a similar type of disease is also clear. Beyond that, it seems probable that the high blood-pressure seen as a symptom in the more acute inflammatory affections of the kidney must be dependent upon other causes than this particular arteriolar disease.

The foregoing study seems to me to show clearly, if it shows anything, that the symptom pictures presented may consist of almost any set of combinations in any of these types of disease, and that clinically a satisfactory anatomical diagnosis is almost impossible. Further study by tests of renal function may help in differentiation, but for the present the physician who goes to the autopsy table expecting to be right as to the gross or minute anatomical lesions in these patients with high blood-pressure will frequently meet with disappointment. For this reason—because it emphasizes both the existence of real anatomical lesions and the

[1] Janeway, Theodore C. "Nephritic Hypertension: Clinical and Experimental Studies," Amer. Jour. Med. Sci., 1913, cxlv, 625.

[2] Gull and Sutton. "On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with contracted Kidney," Med.-Chi. Trans., 1872, lv, 273.

[3] Jores. Kritisches zur Lehre von der Nephritis and den Nephropathien, Med. Klinik., 1913, ix, 18.

relation to them of the unifying physiological disturbance—I prefer for the present to speak of all these patients as cases of hypertensive cardiovascular disease. Where this condition becomes engrafted on an obvious primary inflammatory nephritis, I consider it secondary hypertensive cardiovascular disease. Where it originates insidiously and the urinary changes are part and parcel of the picture from the start, or follow later, I consider it primary hypertensive cardiovascular disease. The results of these processes entail danger from the standpoint of the heart, the arteries, especially the cerebral arteries, or of eventual kidney atrophy below the factor of safety for the human kidney.

XII. Conclusions. 1. The most prominent symptoms associated with high blood-pressure are circulatory, rather than renal. The disease underlying high arterial pressure is predominantly a disease of the circulatory system, and is best designated hypertensive cardiovascular disease, either primary, or secondary when preceded by an inflammatory nephritis.

2. Death in this type of cardiovascular disease among patients in private practice occurs in the following ways, arranged in the order of their frequency: (1) by gradual cardiac insufficiency, (2) with uremic symptoms, (3) by apoplexy, (4) from some complicating acute infection, (5) in an attack of angina pectoris, (6) from purely accidental and unrelated causes, (7) in a paroxysm of acute edema of the lungs, (8) after the manner of cachexia.

3. The early symptoms associated with hypertensive cardiovascular disease have an important prognostic significance which can be utilized therapeutically, particularly for the institution of safeguarding treatment.

4. The early occurrence of symptoms of myocardial weakness, especially dyspnea, indicates more than 50 per cent. probability of an eventual death by cardiac insufficiency. In these patients, to safeguard the heart is the main therapeutic indication.

5. The early occurrence of anginoid pain on exertion does not indicate a probability of death in an anginal paroxysm for more than one-third of the patients. It does indicate a probable cardiac death of some type. The therapeutic indications here are similar to the foregoing, except as modified by the existence of syphilitic

aortitis. Anginal attacks as compared with other cardiac symptoms do not materially affect the expectancy of life.

6. Polyuria, particularly if nocturnal, indicates the probability of a uremic death for more than fifty per cent. of the patients. It is not essential to safeguard the heart in these patients, unless associated cardiac symptoms exist.

7. Headache, especially that heretofore described as typical, indicates the probability of a uremic death for more than 50 per cent. of the patients and of death from apoplexy for a considerable number of the remainder. The therapeutic indications are similar to those of polyuria.

8. Loss of flesh, if marked and progressive, is a symptom of bad prognostic import.

9. The relation of the height of the blood-pressure to prognosis is doubtful. Systolic pressures persistently well above 200 mm. (Hg.) seem to indicate a greater probability of death by uremia or apoplexy. The exact height of the blood-pressure does not seem to have much bearing upon the expectancy of life.

10. The average duration of life in this group of patients, after the onset of symptoms associated with high blood-pressure, has been four years for the men and five for the women. One-half of the whole number of deceased died during the first five years. One-quarter of the number lived between five and ten years, and the remaining quarter over ten years from the appearance of the first symptom. The existence of this considerable number of patients living for a long period of time suggests the need of great caution in making a prognosis as to expectancy of life.

In conclusion, I wish to express my indebtedness to my secretary, Miss Anna L. von der Osten, for the statistical work extending over a year and a half represented by these studies; and to acknowledge with thanks the helpful suggestions on statistical problems afforded by Dr. Leonard P. Ayres, of the Russell Sage Foundation.

DISCUSSION

Dr. R. C. Cabot: Out of the many points of interest suggested by this valuable contribution, I wish to remark upon the fact that three deaths from pernicious anemia were recorded. We would hardly meet with so many among an equal number of average people.

Dr. Henry Sewall: I wish Dr. Janeway would indicate whether he believes that the pulse-pressure gives any information of prognostic value? Personally, I feel that this has some clinical importance.

Dr. Jos. L. Miller: Have Dr. Janeway's patients who lost weight also lost their appetite? I have felt that in these cases some fault of metabolism is operative.

Do Dr. Janeway's patients show a tendency to a gradual increase of blood-pressure? I have not found this to be usual.

I think we should always keep in mind that nervous factors, such as grief or anxiety, will often produce a striking temporary rise of pressure.

Dr. W. S. Thayer: Such a report as this just presented by Dr. Janeway may be of immense value in the hands of the profession as a means of allaying the fears of the public as to the danger of increased blood pressure.

Dr. Henry Jackson: I for one am glad to hear these statements made by Dr. Janeway. There is great satisfaction in knowing that high pressures may be safely maintained for a long time. The results of Dr. Janeway's study seem to confirm my feeling that a falling pressure, in a hypertensive case, may be a serious prognostic portent.

Dr. C. F. Hoover: I am interested in the headaches that appear with arterial hypertonus. Such headache may have one of three explanations: (1) It is a toxic headache, due to renal insufficiency; this is infrequent alone, perhaps; (2) it is due to cerebral ischemia; (3) it is due to cerebral hyperemia.

If in a case with fibrosis of the cerebral vascular system there is an intercurrent loss of splanchnic hypertonus, headache and weakness will result from cerebral ischemia.

In cases of the third variety, in which, in the absence of cerebral fibrosis, there is cerebral hyperemia, the headache will be increased by the administration of nitroglycerin, but may be relieved at once by inducing nausea.

It is possible for complete suppression of urine to result from hypertension of the renal system. This was shown by the case of a patient

brought into the hospital in coma, which was thought to be uremic. He was anuric for a number of hours, but after treatment with packs he began to secrete urine which on examination was found to be entirely normal. Later this man became anuric again, went into coma, and died.

Dr. A. McPhedran: It is interesting to know the details of the behavior of the blood-pressure in any given patient; it is apt to be so variable. Were one or many observations of the pressure made in Dr. Janeway's cases?

Are there any observations recorded in the full paper as to the value of the nitrites in reducing pressure?

Dr. Janeway: No mention of the pulse-pressure was made in the paper because within the years covered by the series of cases the method of auscultatory estimation of the diastolic pressure has come into use and exact comparison could not be made.

The cases mentioned as dying of anemia had "progressive" anemia, not "pernicious" anemia as understood by Dr. Cabot. These cases belong with the loss of weight cases; there are two groups of these: (1) Those losing weight from a slow terminal anemia, and (2) the elder arteriosclerotic group, among whom the loss of weight is due to failure of nutrition dependent on sclerotic changes in important organs. One important cause of loss of weight in certain cases is achylia gastrica with anemia.

There are two groups of hypertensive cases: (1) Pure arteriosclerosis, and (2) presenile sclerosis.

When a sclerotic nephritis is superadded upon arteriosclerosis the pressure begins to rise and the prognosis becomes increasingly bad.

A falling blood-pressure in a patient who has had a pressure habitually high is of bad omen.

The headache problem is very much involved, and no attempt was made to discriminate between the kinds of headache occurring in this series. But those cases in which headache, independent of renal insufficiency, was a prominent symptom gave signs of disease of the cerebral vessels. Such headaches are not relieved by nitroglycerin.

As to the nitrites, there are few cases which will not respond to this group of drugs; much depends upon the dosage employed, as the response is very variable. A few cases will not respond at all.

The statistics given in the paper are based on all sorts of cases, observed once or many times over a period of eight or nine years, and they will have to be taken for what they are worth.

A STUDY OF THE URIC ACID IN THE BLOOD IN GOUT BY THE METHOD OF FOLIN AND DENIS

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(From the Massachusetts General Hospital and the Biochemical Laboratory of Harvard University)

Within the past decade much value has been attached by German clinicians to the demonstration of uric acid in the blood in the diagnosis of gout. Even for qualitative analysis large amounts of blood have been necessary and attempts to estimate the quantity of uric acid in the blood have not been satisfactory owing to faulty methods of analysis. Many have shared the desire to which His[1] recently gave expression that some method might be devised for the diagnosis of gout that would be of wider application and greater exactness. This need has been fulfilled by the discovery of a new method for the determination of uric acid in the blood by Folin and Denis.[2] The description of the method was published in January, 1913. It gives accurate results and requires only 15 to 20 c.c. of blood. The study of uric acid in the blood can be divided historically into three stages. (1) The demonstration of uric acid in the blood of gouty patients by Alfred Baring Garrod in 1848. (2) The use of rough quantitative methods. (3) The introduction of the exact quantitative method of Folin and Denis in 1913.

Garrod's first observations were made in the summer of 1847 and the following year after he had repeated them upon several cases of gout with uniform results he published his findings in

[1] Die Behandlung der Gicht und des Rheumatisms mit Radium, Berl. klin. Woch., 1911, xlviii, 197.

[2] A New Colorimetric Method for the Determination of Uric Acid in Blood, Jour. Biol. Chem., 1913, xiii, 469.

the Transactions of the Medico-Chirurgical Society.[1] At that time he drew the conclusion that "the blood in gout always contains uric acid in the form of urate of soda which salt can be obtained from it in crystalline state." Eleven years later he wrote[2] that the only alteration he would be disposed to make in this statement would be to append the words "in abnormal quantities."

Great credit is due to Garrod for the care and thoroughness with which he carried out his early studies at the University College Hospital in London at a time when the facilities for such an investigation must have been meagre. His method of demonstrating uric acid was as follows: The blood was allowed to clot. Then 67 gm. (1000 grains) of the clear serum were dried on a water bath, reduced to powder, boiled with alcohol, and treated with boiling distilled water. "When a few drops of the watery solution were evaporated almost to dryness with nitric acid, and held over the vapor of ammonia, distinct evidence of uric acid was afforded by the production of the beautiful purple tint of murexide or purpurate of ammonia; and when reduced to a thin syrupy consistence, and a few drops of hydrochloric acid added, and set aside, in a few hours crystals of uric acid were deposited with the characteristic forms of that body."

"From another quantity of blood drawn soon after the first, 1000 grains of serum were taken and treated in the same manner, except that no hydrochloric acid was added. The concentrated watery solution was allowed to stand for some hours, when on examination very numerous tufts of crystals were found deposited on the sides of the vessel and surface of the fluid. These crystals were proved to consist of urate of soda; they yielded rhombs of uric acid on the addition of a stronger acid, and when incinerated left an ash, alkaline in reaction, soluble in water, and not answering to the tests for potash."

Garrod attempted a quantitative analysis and obtained from the first patient the equivalent of 5 mg. of uric acid per 100 gm.

[1] Garrod, Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease, Medico-Chirurgical Transactions, London, 1848, xxxi, 83.

[2] Garrod, The Nature and Treatment of Gout and Rheumatic Gout, London, 1859, p. 107.

of blood serum. He regarded this quantity as much under that really present.

This method employed by Garrod does not seem to have been used subsequently. Petren[1] could find no reference in the literature to its employment. Unfortunately Garrod[2] later introduced the untrustworthy thread test as a clinical method for the diagnosis of gout. This was widely used.

The first attempt to make a series of quantitative estimations of the uric acid in the blood of gouty subjects was made by G. Klemperer.[3] In three patients during attacks he determined the amount of uric acid to be 6.6 mg., 8.8 mg., and 9.15 mg. per 100 c.c. of blood.

Magnus-Levy[4] made 34 examinations of the blood on 17 gouty individuals, and found the amount of uric acid to range from 2.1 to 9.5 mg. per 100 c.c. of blood.

Brugsch and Schittenhelm[5] found that uric acid was still present in the blood of gouty patients after they had been on a purin-free diet for weeks and months. They regard endogenous urikemia as a constant symptom of gout. Brugsch[6] in his latest communication (1913) states that there is no plainly demonstrable uric acid in the blood when a healthy individual is on a purin free diet, hence the diagnostic importance of the presence of endogenous uric acid in the blood of gout. Uric acid is present not only in gout, but has been found in the blood in certain forms of nephritis, leukemia, pneumonia after the crisis, and after the application of Röntgen rays to the skin, even when the patients were on a purin-free diet.[7]

The German investigators used either the ammoniacal silver method or the cupric bisulphite method for precipitating uric acid.

[1] Ueber das Vorkommen von Harnsäure in Blute bei Menschen und Säugethieren, Arch. f. exp. Path. u. Pharm., 1898, xli, 265.

[2] On the Blood and Effused Fluids in Gout, Rheumatism, and Bright's Disease, Medico-Chirurgical Transactions, London, 1854, xxxvii, 49.

[3] Zur Pathologie und Therapie der Gicht, Deutsch. med. Woch., 1895, xxi, 655.

[4] Ueber Gicht, Zeitschr. f. klin. Med., 1899, xxxvi, 353.

[5] Zur Stoffwechselpathologie der Gicht, I Mittheilung, Zeitschr. f. exp. Path. u. Ther., 1907, iv, 444.

[6] Brugsch in Kraus and Brugsch, Spezielle Pathologie und Therapie innere Krankheiten, Berlin, 1913, i, 192.

[7] Brugsch and Schittenhelm, Der Nukleinstoffwechsel und seine Störungen, Jena, 1910, 65.

The procedure of Kruger and Schmid has been chiefly employed. By means of these methods the presence of uric acid in gout and the other diseases just mentioned was definitely demonstrated. But to obtain even a qualitative test in blood rich in uric acid it was necessary to take more than 75 c.c. of blood. In the cases in which positive results were obtained by Brugsch and Schittenhelm 100 to 200 c.c. of blood were removed by venesection. By the use of these methods G. Klemperer,[1] and von Jaksch,[2] failed to find any uric acid in normal blood. Abels[3] and Petren[4] obtained very slight amounts of uric acid.

Folin and Denis[5] state that the methods employed by earlier investigators would fail to reveal moderate amounts of uric acid (1 to 2 mg.) and yet would give too high figures if any uric acid at all were found.

Various modifications of the precipitation method for determining the quantity of uric acid in the blood have been proposed recently by Kowarsky,[6] Gudzent and Apolant,[7] Schneller,[8] and Bass and Wiechowski,[9] but all are open to criticism. The claim of Bass and Wiechowski that by their method they could determine the small amount of uric acid present in the blood of healthy individuals on a purin-free diet seems very doubtful in view of the fact that they could not demonstrate by their method the diminution of the uric acid in the blood which occurs after the administration of atophan.

Brugsch and Schittenhelm[10] viewed their own quantitative

[1] Zur Pathologie und Therapie der Gicht, Deutsch. med. Woch., 1895, xxi, 655.
[2] Ueber Uricacidämie, Deutsch. med. Woch., 1890, xvi, 741.
[3] Ueber Harnsäure im Blut und einigen Organen, und Geweben, Wien. med. Jahrb., 1887, lxxxiii, 479.
[4] Ueber das Vorkommen von Harnsäure im Blute bei Menschen und Säugetieren, Arch. exp. Path. u. Pharm., 1898, xli, 265.
[5] Protein Metabolism from the Standpoint of Blood and Tissue Analysis, Sixth paper, On Uric Acid, Urea, and Total Non-protein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, xiv, 41.
[6] Ein Method zum Nachweis und zur quantitativen Bestimmung von Harnsäure in relativ kleinen Blutmengen (10 c.c.), Deutsch. med. Woch., 1911, xxxvii, 1112.
[7] Eine einfache Methode zum Nachweis von Harnsäure im Blut und anderen kolloiden Flüssigkeiten, Deutsch. med. Woch., 1912, xxxviii, 603.
[8] Zur Methodik der Harnsäurebestimmung im Urin und Blut, Zeitschr. f. exp. Path. u. Ther., 1913, xii, 2.
[9] Ueber den Purinstoffgehalt des Blutes und seine Bestimmung, Wiener klin. Woch., 1912, xxv, 863.
[10] Zeitschr. f. exp. Path. u. Therap., 1907, iv, 440.

analyses with some suspicion. They regarded the determination of as little as 1 to 3 mg. as practically impossible. Folin and Denis[1] state that a procedure recommended by Brugsch and Schittenhelm[2] of treating the blood with hot caustic potash solution, 2 to 5 per cent., would destroy anywhere from 30 per cent. to all of the uric acid originally present.

The method of Folin and Denis is based on a color reaction so delicate that one part of uric acid in a million parts of water can be recognized. The determinations can be made in 25 c.c. of blood or less, according to the amount of uric acid present. If the blood is rich in uric acid an analysis is possible with only 10 c.c. of blood.

Folin and Denis[3] have not published any figures on the uric acid content of strictly normal blood. In 38 unselected cases admitted to the Psychopathic Hospital in Boston the uric acid content with the patients on a mixed diet was below 1 mg. per 100 grams of blood in 5 cases, between 1 and 2 mg. in 22, and above 2 mg. and below 4 mg. in the remaining 11 cases. They believe that figures ranging from 1 to 2 mg. per 100 grams of blood are well within the normal limits. No relationship was found between the amount of uric acid and the amount of urea or total non-protein nitrogen in human blood. Unfortunately no figures are yet available on the uric acid content of healthy individuals on a purin-free diet.

Folin and Denis analyzed the blood from 5 cases of gout. Three of these were under my observation and are described in more detail in this paper. Folin and Denis found the amount of uric acid in these cases ranged from 3.5 mg. to 5.5 mg. per 100 grams of blood.

In 2 cases of leukemia the amounts of uric acid in the blood were 3.1 mg. and 4.1 mg. In 2 cases of lead poisoning 4.7 mg. and 4.8 mg. In one case of renal calculus, 5.2 mg., the stones were

[1] A New Colorimetric Method for the Determination of Uric Acid in Blood, Jour. of Biological Chemistry, 1913, xiii, 469.

[2] Zeitsch. f. exp. Path. u. Therap., 1907, iv, 441.

[3] Protein Metabolism From the Standpoint of Blood and Tissue Analysis, Sixth paper, On Uric Acid, Urea, and Total Non-protein Nitrogen in Human Blood, Jour. Biol. Chem., 1913, xiv, 32.

composed of uric acid. In 11 cases of nephritis the figures ranged from 1.1 mg. of uric acid to 3.9 mg.

The uric acid analyses of the blood reported in this communication, 11 cases of gout, were made by Dr. Denis and Dr. Lyman in Professor Folin's laboratory. All the cases but one were from the wards and out-patient department of the Massachusetts General Hospital, and were available for study through the kindness of Professor Edsall.

MILLIGRAMS OF URIC ACID PER 100 GRAMS OF BLOOD IN CASES OF GOUT

Case	Patient	Age	Date of examination	Ordinary diet		Purin-free diet		After administration of atophan in attack
				Attack	Interval	Attack	Interval	
I	A. B.	66	Oct. 15	....	5.5[1]			
			Nov. 3	....	5.5[1]	....	3.4[1]	
II	E. T.	30	Nov. 9	....	3.5[1]			
			Apr. 14	....	5.0			
III	J. K.	45	Nov. 12	....	4.4[1]			
			Apr. 17	....	5.5			
IV	D. H.	45	Jan. 20	....	4.0			
V	D. N.	58	Mar. 21	....	....	3.1[2]		
			Mar. 23	....	....	....	....	2.2[2]
VI	J. H.	36	Mar. 27	5.7[2]	....			
			Apr. 1	....	....	....	....	2.2[2]
VII	G. K.	55	Mar. 27	....	....	2.4[2]		
			Apr. 1	....	....	....	....	2.1[2]
			Apr. 16	....	....	3.6[2]		
			Apr. 21	....	....	5.1[2]		
			Apr. 25	....	....	....	....	1.6[2]
VIII	R. S.	45	Apr. 12	....	3.9			
IX	E .D.	61	Apr. 14	....	4.5			
			Apr. 21	....	....	....	....	1.2
X	J. U.	62	Apr. 14	....	3.9			
XI	W. L.	59	Apr. 24	....	3.1			

ABSTRACTS OF CLINICAL RECORDS

CASE I.—A. B., aged sixty-six years. No occupation. *Chronic gout.* A great many attacks of gout from 1877 to 1912. Elbows, knees, and feet chiefly affected. Great toe often involved. Alcohol to excess. No deformity of joints. No tophi. Hypertonia. Cardiac insufficiency. Urine contained a slight trace of albumin and hyaline casts. From the spring of 1912 diet was poor in purins. Attack of gout in September, 1912. At the time of the first blood examination (October 15, 1912) he was taking a small amount of meat or fish daily. Uric acid then 5.5 mg. From October

[1] Reported previously by Folin and Denis.
[2] Reported previously by Folin and Lyman.

15 to November 3 he was on a purin-free diet. Second blood examination made November 3, 1912; uric acid content 3.4 mg. Endogenous uric acid output from February 27 to March 7, 1912 ranged from 0.32 gm. to 0.66 gm.

Case II.—E. T., aged thirty-two years. Painter. *Acute gout.* In February, 1911, pain and swelling in knee and great toe. Duration three weeks. No tophi. Urine normal. In October, 1912, had alcoholic gastritis. Blood on November 9, 1912, contained 3.5 mg. of uric acid. Severe attack of gout in January, 1913. Blood on April 14, 1913, contained 5.0 mg. of uric acid. Patient was on a mixed diet.

Case III.—J. K., aged forty-five years. Teamster. *Acute gout.* Severe attacks of acute gout in 1908, 1910, 1911, and 1912. Both feet affected. Pain most severe at night. Has taken alcohol freely for years. Tophi in ears. Joints not deformed. No atherosclerosis. No nephritis. Blood removed November 12, 1912, contained 4.4 mg. uric acid per 100 grams of blood. In March, 1913, attack of gout. Blood withdrawn April 17 contained 5.5 mg. He claimed he has been on a diet that was nearly purin-free for three days.

Case IV.—D. H., aged forty-five years. Policeman. *Chronic gout.* Four attacks of gout in the great toe since 1908. In January, 1911, pain in the knees. In July, 1912, severe pain in the left thigh, over left patella, and right wrist. Pain and swelling of left wrist in October, 1912. In January, 1913, pains in the muscles of the thigh and calf. No tophi. No deformity of joints. Urine free from albumin and sugar.

Case V.—D. N., aged fifty-eight years. Negro. Waiter. *Acute gout.* In November, 1912, pain in the right foot, later pain in the right leg below the knee. On March 6, agonizing pain in the right foot. On March 13, it was localized in the great toe. Coronary sclerosis. Heart enlarged to the left. Blood pressure 190 mm. of mercury. No tophi or deformity of joints. Urine contained a very slight trace of albumin and a few hyaline casts. Admitted to Dr. Edsall's wards on March 18, and placed on a purin-free diet. Blood on March 21 contained 3.1 mg. of uric acid. Output of endogenous uric acid in urine from March 25 to 29 ranged from 0.12 to 0.25 gm. Three days after feeding of 300 grams of roast beef the uric acid in the blood rose to 6.2 mg.

Case VI.—J. H., aged thirty-six years. No regular work. *Acute gout.* He has been a heavy drinker for many years. First joint symptoms in January, 1913. Pain in muscles of lower leg followed by pain, redness, and swelling of both great toes. Attack lasted four or five days. On March 23 inflammation developed in right arm, elbow, hand, right knee, and calves of legs. Later great toes and both feet became involved. Heart normal. No nephritis. Tophi in both ears and in lower right eyelid. Metatarsophalangeal joints of both great toes red and swollen and tender. Swelling and tenderness of the right olecranon and left wrist. Blood on

March 27 contained 5.7 mg. of uric acid per 100 grams of blood. Patient was placed on a purin-free dict March 29. On March 29 atophan 1 gram was given after each meal. On April 1 blood contained 2.2 mg. of uric acid. April 4, atophan discontinued. The uric acid output in the urine was determined daily from March 28 to April 4 and it ranged from 0.06 to 0.44 gm.

Case VII.—G. K., aged fifty-five years. Butcher. *Chronic gout.* Has drunk beer and whisky for many years. Many attacks of gout during the past fifteen years. Fingers, hands, great toes, feet, ankles, elbows, and knees have been involved. For ten years there has been pain and stiffness in the hands, less constantly in the feet. Great swelling and deformity of the fingers. Olecranon processess of both elbows the seat of hard and bone-like nodes. Right olecranon bursa distended with fluid. Marked swelling of both patellæ similar to that of the olecranons. Some enlargement of the metatarso-phalangeal joints of both great toes. Tophi in fingers and tendo Achillis of both feet, none in the ears. Soft fluctuating area about 5 cm. in diameter on dorsum of right hand. When admitted to Dr. Edsall's wards on March 26 his temperature was 38.8° C. He had several febrile periods during his stay in the hospital. No albumin in urine except on March 27 and 28. Some hyaline and granular casts found even when urine was free from albumin. Uric acid crystals found in six out of ten examinations. Placed on purin-free diet on March 26. On March 27 blood contained 2.4 mg. of uric acid. April 6 fed 272 grams of roast beef plus purin-free diet. April 7, blood at noon contained 3 mg. uric acid. April 16, blood contained 3.6 mg. uric acid. April 21, blood contained 5.1 mg. Atophan was given 3 gm. a day, and on April 25 the uric acid has dropped to 1.6 mg. From March 28 to March 31 uric acid output ranged from 0.56 gm. to 0.64 gm. in spite of the purin-free diet. On April 10 material from soft, swelling (gouty abscess) on dorsum of right hand aspirated and found to contain crystals of sodium urate.

Case VIII.—R. S., aged forty-five years. *Acute gout.* Repeated attacks of gouty inflammation of the great toe since 1903. Last attack in February, 1911. He was then confined to bed for two weeks. He takes alcohol, but claims in moderation. Urine in April, 1913, contained a slight trace of albumin; no casts (single examination). Heart normal. Blood on April 12, 1913, contained 3.9 mg. of uric acid. The patient was on a mixed diet.

Case IX.—E. D., aged sixty-one years. Barber. *Chronic gout.* For some years prior to 1894 he drank ten to fifteen glasses of whisky a day. First attack of gout in 1894 involving several joints, but especially the great toe. Every winter since then has been invalided for about three months with "rheumatism" which has attacked both knees, wrists, and joints of fingers and "has gone from his toes to his shoulders." The pain was greatest at night "requiring morphine." When seen on April

14, 1913, he was just recovering from an attack that had confined him to his house for five weeks. Shoulders, elbows, knuckles, and ankles swollen and painful. More swelling of joints of upper extremities than of those of the legs. Unable to work at his trade owing to pain in the feet since June, 1911. The entire tarsus has been involved. Hallux no more painful than other parts of the foot. On April 14, 1913, the blood pressure was 198 mm. of mercury. Urine free from albumin and sugar. Seven tophi in the right ear and three in the left. Acicular crystals found on microscopical examination. Blood on this date contained 4.5 mg. of uric acid. He was then on a mixed diet. Later on a purin-free diet and after the administration of atophan the uric acid fell to 1.2 mg.

Case X.—J. U., aged sixty-two years. *Chronic gout.* First attack of gout in 1896. Occasional mild attacks since then. Large toe chiefly affected. Tophi present in the ears since 1899. Coronary sclerosis. Angina pectoris since 1909. Stricture of urethra. No nephritis. In the latter part of March, 1913, he had an attack of gout. Left big toe swollen and painful. Some pain in ankle and knee. Patient did not restrict his diet. On April 13 ate steak and a boiled dinner. On April 14, blood contained 3.9 mg. of uric acid.

Case XI.—W. L., aged fifty-nine years. *Chronic gout.* Many attacks of gout during the past thirty years. Toes, especially great toes, tarsus, muscles of lower leg, and thigh and hands are the parts that have been affected. Admitted to Dr. Edsall's service on account of cardiac insufficiency on April 11, 1913. No nephritis. No deformity of joints, no tophi. During the following week pain, tenderness, and swelling of the right foot developed. This inflammation subsided in a few days. On April 24 the blood contained 3.1 mg. of uric acid. At that time the patient had no symptoms of gout.

Commentary. Hyperurikemia was present in every case of gout studied. In all the cases tabulated the clinical evidence of gout was conclusive. On a mixed diet the amount of uric acid ranged from 2.4 mg. to 5.6 mg. The patient G. K. with the lowest amount had the severest case of gout. His blood at a later examination when he was on a purin-free diet reached as high as 5.1 mg. The largest amount of uric acid found was in the case of D. N. whose blood contained 6.2 mg. of uric acid three days after eating 300 grams of roast beef. The maximum amount reported by Folin and Denis was 5.5 mg. This was found in the blood of my patient A. B. when on a mixed diet. This patient was placed on a purin-free diet and the uric acid fell to 3.4 mg. In the case of E. D. the uric

acid on a mixed diet was 4.5 mg. When placed on a purin-free diet and atophan given the uric acid fell to 1.2 mg. The action of atophan on the uric acid of the blood has been studied by Folin and Lyman,[1] but this observation was not included in their series. The patient R. S. has had no attack of gout for over two years and yet his blood on a mixed diet contained 3.9 mg. of uric acid.

In our study no more uric acid was found during attacks than during the intervals between attacks. Magnus-Levy came to this conclusion after a large series of blood analyses. Garrod had claimed that the amount of uric acid was increased during attacks, and Brugsch in his recent monograph makes the same assertion, but as already pointed out the methods of analysis used by all three investigators were untrustworthy for quantitative results. Brugsch states that in his analyses with patients on a purin-free diet the amount of uric acid during the intervals usually ranged from 6 to 10 mg. During an attack, or immediately preceding one the amount of uric acid often varied between 10 and 20 mg. When gout was complicated by chronic interstitial nephritis Brugsch obtained even during the intervals between attacks 10 to 20 mg. of uric acid or more. My patient A. B. with chronic interstitial nephritis during an interval on a purin-free diet had 3.4 mg. of uric acid, and D. N. who also had a nephritis had only 3.1 mg. of uric aid on a purin-free diet during an attack.

In other pathological conditions the hyperurikemia may equal that of gout.[2] Folin and Denis reported a case of chronic interstitial nephitis in which the uric acid amounted to 3.9 mg. on a mixed diet. In 10 other cases of nephritis the uric acid varied from 1.0 mg. to 2.9 mg. It would be interesting to study the endogenous uric acid of the blood in nephritic cases. In a typical case of arthritis deformans under my observation, the blood was found to contain 4 mg. of uric acid. There was nothing in the clinical history or physical examination indicative of gout. There was no nephritis and hypertonia was not present. The patient was on a mixed diet. The total non-protein nitrogen was 32 mg., and the urea

[1] On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination, Jour. of Pharm. and Exp. Ther., 1913, iv, 539.

[2] Lyman found that his own blood on a mixed diet contained 4.0 mg. of uric acid. He was in good health and had never had gout (Folin and Lyman).

19 mg. Unfortunately there was no opportunity to determine the amount of uric acid on a purin-free diet. In a second case of arthritis of six months' duration in which the only symptoms were swelling and stiffness of the fingers the uric acid of the blood with the patient on a mixed diet was 3.2 mg.; the total non-protein nitrogen 31 mg.; and the urea 14 mg. It is improbable that either of these cases was gout, but the fact should be emphasized that on a mixed diet cases of arthritis that do not present the clinical picture of gout may have a hyperurikemia equal to that in gout.

DISCUSSION

Dr. Solomon Solis Cohen: Does Dr. Pratt feel that his investigations have served to recall uric acid from the realm of romance and poetry to the sober domain of scientific lore?

Dr. R. M. Pearce: We have been using this method of Folin for the study of nephritis. We divided our cases into groups:

(*a*) Non-nephritic group, from which we ascertained that normally the non-proteid nitrogen fluctuates between 15 and 40; the average normal urea content being 0.012 gm.

(*b*) A group of cardiovascular cases, with no definite renal disturbances. In these the results of analysis were practically the same as in group *a*. There was no hypertension in these cases.

(*c*) A group of chronic parenchymatous nephritis cases; in these we found no great change from the normal.

(*d*) A group of cases of chronic interstitial nephritis; here there was a great increase in the retained nitrogen.

(*e*) A group of arteriosclerotic cases. These, also, showed a great increase in retained nitrogen.

(*f*) One case of acute nephritis in which there was a great increase in total nitrogen.

The method as it worked out in our series helps to support the ideas now current that chronic parenchymatous nephritis is not noteworthy for nitrogen retention, but has more to do with retention of salt.

Dr. E. Libman: Ebstein in our laboratory has not found much difference in the nitrogen retention as between chronic parenchymatous and chronic interstitial nephritis; but he has found a great increase of the globulins in the blood in the former variety of nephritis.

Dr. Pratt: I was much interested in the cases reported by Dr. Pearce. Since undertaking this work I have been impressed by the fact that in Boston, at least, gout is a rare disease. I looked over the records of the out-patient department of the Massachusetts General Hospital since 1903, and in some 200,000 cases, I found the diagnosis of gout made only 27 times; when the histories were studied, I felt obliged to rule out 4 of these.

I was taught to recognize gouty tophi by my teacher, Sir William Osler, and in the wards of the Johns Hopkins Hospital they were not infrequent. Curiously enough, since I have been doing this work, three patients have come into the hospital with typical gouty tophi in their ears.

ON THE MECHANISM OF THE CIRCULATORY FAILURE IN DIPHTHERIA

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In the course of acute infections it is well known that the patient may die with symptoms somewhat like those of surgical shock. The blood-pressure falls, the pulse becomes weak and small, the skin is pale or cyanotic about the nose and ears, sweating and vomiting ensue, and with shallow respiration and general collapse the heart stops beating.

The discussion as to the mechanism of this disturbance is so well known that only the briefest résumé need be given here. It had long been thought from clinical observations that the affection might be one of the vasomotor apparatus rather than the heart itself and Romberg, Paessler, Brühns and Müller attempted to prove this in the case of diphtheria, pneumococcus, and pyocyaneus infections by experimental studies. In these studies they relied upon certain methods which aimed to demonstrate that the heart would regain its activity if the failure of the vasomotor apparatus were overcome in some way and that those things which ordinarily caused vasomotor reactions were ineffectual. Thus they found that the mechanical expression of the blood from the splanchnic veins into the heart would restore for a time the aortic pressure and with that the coronary blood supply and thus the nutrition and activity of the heart. The same could be produced by compressing the aorta. Barium chloride still caused the vessels to contract but sensory stimuli had lost their effect. They therefore concluded

that the circulatory failure was not due primarily to injury of the heart but rather to the paralysis of vasomotor centres in the brain which, causing a lowering of arterial resistance, quickly affected the heart throught the diminished coronary supply to the heart wall. Romberg especially pointed out the fact that if the heart were at fault all these tests should fail.

Then Stejskal criticised their methods, showing that abdominal massage could increase arterial pressure even in a dead animal and that its effects are very transient. He believed that the heart itself is directly injured and fails on that account. Gottlieb supported this view to some extent, believing that the withdrawal of blood from the coronary circulation need not kill the heart so rapidly since a heart may be kept for hours after the animal's death and then revived by perfusion. He therefore thought death probably due to respiratory stoppage with subsequent failure of the heart due to its injury by the poison.

Rolly and Paessler later reviewed the subject and seem to admit the force of Stejskal's objections as to the abdominal massage, and though they maintain the idea that the injury to the heart is through malnutrition, they state that it becomes very susceptible to other injuries. Other writers whose papers are referred to below lean to one or the other view or accept the idea that both vasomotor paralysis with its consequences and direct injury to the heart wall occur.

In the course of a study of the mechanical conditions present in aortic insufficiency, a plan was devised by which the influence of the vasomotors might be almost entirely eliminated and the work of the heart studied by itself.[1] This plan consisted in simply dividing the aorta near its root and connecting it with a long rubber tube ending in a curved glass outlet which could be elevated to any height upon a graduated upright pillar. The aortic pressure could in this way be set at any point according to the height to which the heart must drive the blood against the force of gravity. The blood which escaped fell into a cistern and returned through another long tube to the distal part of the aorta. Of course by applying this

[1] W. G. MacCallum, Johns Hopkins Hospital Bulletin, 1911, xxii, 197.

arrangement to an animal in the collapsed condition which follows poisoning with the diphtheria toxin the injurious effects of paralysis of the vasomotors would be removed at once, and if the theory of the Leipzig school be correct, the heart should return to its normal activity and the animal continue to live.

The following protocols will illustrate the results of this experiment:

Dog 1. Weight 8.9 kg., April 25, 1911, 1 A.M. Given 1 c.c. diphtheria toxin intravenously. At 11 A.M. the animal was found lying sick in the cage. Carotid pressure taken at 11.30. Chest opened and circulation arranged as described, the outlet being set at 130 cm. which was the carotid pressure before the operation. The heart beat well for two hours, after which there appeared great edema of the lungs and the heart dilated and stopped. All of the organs were found to be edematous and to show numerous ecchymoses. The heart beat regularly throughout and the output was well maintained.

Dog 6. Weight 6.6 kg., May 3, 1911., 12.45 A.M. Given 0.75 c.c. diphtheria toxin intravenously. At 1 P.M. carotid pressure taken, aorta cut and external circulation arranged. This finished at 1.20 and the heart beat well until 3.10, when there was extreme edema of the lungs and of other organs. In the heart, which was otherwise grossly normal, there were many hemorrhages. Here as in the first case the heart continued active for two hours.

Dog 7. Weight 10.3 kg., May 5, 1911, 12.30 A.M. Given 2 c.c. diphtheria toxin intravenously. At 12 noon dog was apathetic and drowsy. At 2 P.M. vomited and appeared very weak. Artificial or external circulation arranged at 2.40 and heart beat at a pressure of 110 cm. blood until 5.45. At times the heart began to collapse and beat with great excursions, driving out relatively little blood. One dose of digitalin and strychnine was given which restored it to its normal beat. During the latter part of the three hours there were violent general convulsions.

Dog 13. Weight 6 kg., April 2, 1913, 10.30 A.M. Given 3 c.c. diphtheria toxin intravenously. Found very sick at 4 P.M., and at 4.45 the external circulation was arranged after which the heart beat, quite well until 7.20, when the supply of blood failed and the experiment was stopped. There was some irregularity in the action of the heart, but on the whole it beat strongly for two hours and thirty-five minutes.

In order to have a good control observation two dogs of the same size were given the same dose at the same time. It was

intended to show that with the aid of the maintenance of arterial pressure one could be kept alive long after the other had died.

Dog 14 A. Weight, 10560; female.

Dog 14 B. Weight, 10900; male. Each given 4 c.c. diphtheria toxin intravenously at 8 A.M. April 3, 1913, both dogs had vomited and were depressed and weak. At 5 P.M. dog A was found lying stretched out stiffly and not breathing. Heart beating feebly. Artificial respiration was begun. Carotid pressure very low. It was attempted to establish the external circulation, but through an accident the dog died. By this time, 5.35, dog B was almost dead and lay inert. Reflexes were gone, the eyes rolled about, and there were convulsive twitchings. External circulation was established at 5.45 and tracings of the heart beat were taken until 8.35, a period of two hours and thirty five minutes, when the heart stopped apparently only because it finally became necessary to use blood which had been kept several days.

Dogs 15 A and B, weighing respectively 11 and 10.3 kg., were given 4 c.c. diphtheria toxin at 8 A.M., April 8, 1913. At 3.15 both dogs were almost dead, lying quite apathetic, with complete loss of reflexes and occasional convulsions. Dog A, whose blood-pressure as taken from the carotid was very low, about 60 cm. of blood, was arranged with the external circulation and the outflow tube set at 85 cm. The heart beat improved at once and continued from 3.30 to 4.40. In the meanwhile dog B died at 3.20. The character of the pulse of Dog A as seen in the tracing varied spontaneously, being rapid and strong at times and producing an abundant outflow, while at other times there was a slower collapsing beat which propelled relatively little blood to the outflow. After one hour and ten minutes it became distended during a convulsion, and could not be made to beat again. It seemed that in this case at least the heart itself had been injured by the poison.

For comparison normal dogs were subjected to the same operation as shown in the following protocols:

Dog 2. Weight, 6.9 kg. Anesthetized with chloretone April 28, 1911. External circulation complete at 3.30 P.M.; pressure set at 130 cm. blood, which equals about 100 mm. mercury. At 4.45 there was much oozing from cut tissues and heart became distended. Pressure lowered to 53 cm. and heart beat again. Some edema of lungs and of other tissues. Given a dose of digitalin, after which heart beat well until 6.30, when the dog was killed.

Dog 5. Weight, 9.9 kg. Anesthetized with ether May 2, 1911. The external circulation was arranged through one intercostal space at 3.20, and the outflow tube set at 130 cm. of blood. The heart beat well until 6.20, when the dog was killed.

The actual output per minute of each of these hearts cannot be accurately determined from the curves produced by this method because much of the blood circulates through the head and forelimbs, but since the records were all made in the same way it will give some idea of the character of the heart's work after diphtheria poisoning to compare the output from the artificial aorta with that in the case of the normal dogs.

Dog 7 (diphtheria). Weight, 10.3 kg. Outlet set at 110 cm.
Operation at 2.40.
At 3.30, 100 c.c. is delivered in twenty-six seconds.
At 4.00, 100 c.c. is delivered in twenty-eight seconds.
At 4.30, 100 c.c. is delivered in thirty-two seconds.
At 4.35, 100 c.c. is delivered in thirty seconds.
Dog 1 (diphtheria). Weight, 8.9 kg. Outlet at 130 cm.
Operation at 11.30.
At 12.00, 100 c.c. is delivered in eighteen seconds.
At 12.30, 100 c.c. is delivered in nineteen seconds.
At 1.00, 100 c.c. is delivered in nineteen seconds.
At 1.30, 100 c.c. is delivered in eighteen seconds.
Dog 2 (normal). Weight, 6.9 kg. Outlet at 130 cm.
Operation at 3.30.
At 3.50, 100 c.c. is delivered in twenty-one seconds.
At 4.30, 100 c.c. is delivered in twenty and a half seconds.
At 5.45, 100 c.c. is delivered in thirty-four seconds.
Dog 5 (normal). Weight, 9.9. Outlet at 130 cm.
Operation at 3.
At 3.45, 100 c.c. is delivered in thirty-five seconds.
At 4.30, 100 c.c. is delivered in twenty-nine seconds.
At 5.00, 100 c.c. is delivered in thirty seconds.
At 5.30, 100 c.c. is delivered in twenty-nine seconds.
From these it will be seen that the actual work of the diphtheria hearts is at least as good as that of the normal hearts.

It is probable that if the conditions were absolutely perfect and the exposure, use of defibrinated blood, etc., avoidable, it would be possible to keep a normal heart driving the external circulation for a longer time than three hours. It is probable, too, that even under the present circumstances a normal heart treated in the way the hearts of the poisoned animals were treated would beat a little longer and a little more steadily than they. But the difference is

so slight that, while it seems probable from such spontaneous irregularities as occurred in the case of dog 15 A that the heart itself is injured by a large dose of toxin, it is clear enough that it is still able to carry on the circulation for two or three hours against a high pressure—a thing which is vastly different from mere beating in a perfusion apparatus.

It might be objected that the use of fresh blood would restore the heart by washing away the toxin, but in all these experiments the blood of the animal itself was returned to the circulation and is merely diluted. At any rate, Decroly and Ronnse showed that diphtheria toxin injected into the blood stream disappears completely after four to seven minutes, so that the injury is probably determined in some early part of the latent period. Rolly in his experiments found that washing out an isolated heart with fresh blood had no effect in postponing the death of the heart, and apparently this is true. But while Rolly was unable to revive a poisoned heart it proves to be not impossible, as the following protocols show:

Dog 16. May 13, 1911. Isolated heart from normal dog perfused with Ringer's solution beat for two and a half hours at a rate of about 103. Ten drops of diphtheria toxin injected into the circulating fluid caused an immediate increase in rate to 200, after which the heart continued to beat for two hours longer at a rate of about 150.

Dog 17. May 24, 1911. Isolated heart from normal dog perfused and beating for one hour at a rate of 98. At 12.25, 1 c.c. of diphtheria toxin was added to perfusion fluid. This was followed by a marked stimulation of force and rate which rose to 112. The heart continued to beat until 3.30, when, after a period of dissociation of auricular and ventricular beats, it stopped.

Dog 18. May 25, 1911. Weight, 5.7 kg. Given 1 c.c. toxin intravenously at 11.10 A.M. At 6 P.M. carotid pressure low. At 10.30 dog was extremely ill and died at 10.55. Heart found to have stopped beating. It was removed from the body and perfused with Ringer's solution, upon which it began to beat at 11.10 and continued to beat well for one hour and ten minutes.

Dog 19. May 25, 1911. Weight, 5.9 kg. Given 1 c.c. diphtheria toxin at 11.30 A.M. At 5.45 P.M. dog was killed with ether and heart excised and perfused with Ringer's solution. From 6.45 to 10.55 it beat strongly and regularly at a rate of about 90 to 110.

Dog 20. May 25, 1911. Weight, 6.8 kg. Given 1 c.c. diphtheria toxin at 11.45 P.M. At 1 P.M. next day dog was nearly dead. Killed at 1.35 and

heart perfused. The rate was somewhat irregular, varying from 44 up to 110, but for the greater part of the next two hours it beat strongly at about 62, stopping at 4.50 P.M.

Dog 21. May 28, 1911. Weight, 7.8 kg. Given 2 c.c. of diphtheria toxin intravenously at 9.45 P.M. At 11 A.M. next morning the dog was found dead, although alive and apparently fairly well a few minutes before. Heart excised but could not be started in perfusion apparatus until 11.50. At first there was fibrillation, but this was stopped by injection of potassium chloride, after which it beat somewhat irregularly until 2.15 P.M., a period of two hours and twenty-five minutes.

Dog 22. May 30, 1911. Weight, 8.7 kg. Given 2 c.c. diphtheria toxin at 11 P.M. Next day at noon dog died; splanchnic vessels much dilated. Heart perfused at 12.15 and beat fairly well for three hours and forty minutes, becoming edematous at last. For most of the time the rate was 96 to 100, but several times a spontaneous heart-block occurred, with a 1:2 rhythm, which each time suddenly changed back to the 1:1 rhythm.

Dog 23. May 30, 1911. Weight, 8.2 kg. Given 1.5 c.c. diphtheria toxin at 11 P.M. Next day at 3.15 P.M. dog was evidently dying. Was killed with ether and heart excised and perfused. Perfusion began at 4 P.M., and heart beat with varying rate until 7.20, a period of three hours and twenty minutes.

Dog 24. June 1, 1911. Weight, 7 kg. Given 2 c.c. diphtheria toxin at midnight. At 11 A.M. next day dog was *in extremis*. Carotid pressure very low. Etherized, heart excised and perfused. It beat slowly from 11.20 to 2.25, about three hours, at a rate of about 52.

Dog 25. June 2, 1911. Weight, 7.2 kg. Given 2 c.c. diphtheria toxin at midnight. At 1.15 next day dog was very sick. Alcohol by stomach tube had no effect upon blood-pressure, which sank until the dog's death at 2 P.M. At 2.10 heart was perfused and beat normally at a rate of about 94 for three hours and thirty minutes, stopping at 5.40.

Dog 26. June 3, 1911. Weight, 8.9 kg. Given 2 c.c. diphtheria toxin at 11.15 P.M. Next morning at 9.30 dog was found dead, but not cold. Rigor beginning. At 9.45 the excised heart was perfused and beat until 10.40, at the rate of about 100, rather feebly and irregularly.

In all these hearts the beat is rather feeble as compared with that of the perfused normal heart, and fibrillation seemed very likely to occur. The note reads: "There is no comparison between the perfused normal heart and the diphtheria hearts all of which are feeble and apt to go into fibrillation." Nevertheless, although one may receive the impression that the hearts from the poisoned animals are rather weak and apt to be irregular, it is clear that

they continue to beat for several hours after they have shown every sign of failure in the body of the dying animal, if only the pressure of nutritive fluid be maintained in the coronary arteries. Indeed, the animal may be allowed to die and an hour after its death the heart can be revived and will beat for a long time. All of this seems to show fairly well that the death which occurs in the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although that may play some part in the process.

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SECONDARY TUMORS OF THE LUNG AND PLEURA

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(Abstract)

Dr. Herrick reported on certain clinical features of secondary tumors of the lungs and pleura. He cited a case of secondary osteosarcoma of the lung in which nearly five years had elapsed from the time of amputation of the leg to the development of symptoms showing lung involvement. After a slight cough of a few days' duration there was profuse hemoptysis and the entrance of blood and air into the pleural cavity. After a critical period of several days the severe anemia gradually improved and the patient was able to be up and about, dying several months later with typical pressure and constitutional symptoms of intrathoracic tumor. The long period of comparatively good health after the operation on the primary tumor (a round-celled osteosarcoma) and the occurrence of hemopneumothorax due to new growth are worthy of note.

In a second case, by radical operation, a chorio-epithelioma (malignant syncytioma) of the uterus had been removed some two years before a massive pleural effusion appeared. The fluid subsided and about a year later severe pain in the back and legs became pronounced. Later, paraplegia and the autopsy showed this to be due to a tumor of the lower cord. The pleura was the seat of a rather large and diffuse growth. All the tumors were of the same nature as the primary uterine tumor that had been removed. Secondary manifestations of malignant syncytioma are usually much earlier. The effusion into the pleura evidently marked the eruption of secondary tumors into that cavity. The rapid appearance of a large pleural effusion due to neoplasm with its rapid disappearance is worthy of note.

PRIMARY INFECTION WITH TUBERCLE BACILLI, WITH SPECIAL REFERENCE TO THE THORACIC GLANDS

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In this study of the probably commonest mode of entrance of tubercle bacilli into the human body, in which I am trying to show that the tracheobronchial glands are in most instances the seat of the initial lesions and the means of dissemination of the tuberculous process to the lungs, four lines of investigation have been carried on.

1. (*a*) A study of the reports of autopsies on children dying of tuberculosis.

(*b*) A study of the location of the lesions of obsolete tuberculosis from 3000 autopsy records of the Massachusetts General Hospital. (Drs. J. H. Wright, Oscar Richardson.)

2. U. S. Meat Inspectors' reports showing frequency and location of tuberculosis in hogs and cattle.

3. (*a*) Instantaneous *x*-ray plates of 200 cases of clinically early lung tuberculosis in young women.

(*b*) Clinical examination and *x*-ray plates of 15 children of markedly tuberculous parents.

(*c*) Review of *x*-ray interpretation of plates in 98 cases of clinically doubtful pulmonary tuberculosis. (Massachusetts General Hospital *x*-ray department, Drs. Dodd and Holmes, January 1, 1913, to May 1, 1913.)

(*d*) *x*-ray interpretation in 19 cases sent for plates when gland tuberculosis was suspected. (Massachusetts General Hospital, *x*-ray records.)

4. (*a*) Review of experimental data with reference to von Behring's theory of ascending infection through lymph channels from intestinal lesions.

(*b*) Experiments with the dissemination of dead carbol-fuchsin stained tubercle bacilli injected into rabbits in:

1. Lateral ear vein showing characteristic lung lesions.
2. Loose tissue around cervical glands.
3. Right foreleg.
4. Intraperitoneally.

1. (*a*) *The Prevalence of Primary Gland Involvement.* Karlson[1] who reports the examination of 15,219 children of school age in Stockholm found:

	Per cent.
Signs of lung tuberculosis in	1.60
Suspicious signs of lung tuberculosis in	2.20
Bone and joint tuberculosis in	0.57
Enlarged glands in	65.00
Presumably tuberculous glands in	10 to 30.00

Escherich[2] from a clinical and anatomical study concludes that in aërogenous tuberculosis of the lung with walling off and caseation of *bronchial lymph glands* and terminal rupture into the blood stream or bronchus we have the typical and characteristic course of tuberculosis of infancy.

Ghon,[7] on the other hand, regards aërogenous lesions of the lung tissue itself as primary and the most frequent source of the disease, and in 184 autopsies on children with lung tuberculosis he thought the lung lesions showed a more advanced state than the glands, and held that the fan-like arrangment of the lesions suggested a spread from the pulmonary focus to the hilus as the course of the lymph stream was in that direction. A hematogenous route he excluded because in 85 per cent. of the cases only one lesion was found instead of the multiple ones usual in metastatic processes.

These observers present facts and suggest interpretations that are not in accord, and indicate a variance in opinion regarding the entrance of tuberculosis into the human body and its spread. It is generally recognized that moist or dry particles of tuberculous matter contained in the inspired air are stopped in the trachea and large bronchi, and may pass through the uninjured and intact wall into the lymphatics and be deposited in the glands.

The frequency which will be shown of gland involvement as compared to any or all other primary lesions makes pertinent the suggestion that lymphatic defence is occasionally overcome either through massive invasion or diminished resistance, and, in fact, the lymphatic defence once sufficiently overcome may lead to its actual participation in the invasion. The massive tubercular pneumonias from rupture of glands into bronchi and the hematogenous route in miliary tuberculosis of one lung or part of one lung alone are due to this cause.

There remains still the vast majority of cases of pulmonary tuberculosis which present a picture of exceedingly mild trouble seemingly localized in a small area. Many of the extensive involvements also have been so insidious in their course and progress as to suggest an exceedingly insignificant beginning. It is an explanation of the beginning and progress of this type of the disease that is attempted in this paper.

Allbrecht[3] in 2000 autopsies on children reports 6 per cent. of primary tuberculosis in the intestinal tract and glands, whereas in a "great majority" it was primary in the lung. In no case was there cervical lymph-gland tuberculosis without tuberculosis of lungs or tracheobronchial glands.

Wollstein[4] from the N. Y. Babies' Hospital material says "even in childhood the respiratory tract is more frequently the entrance point than is the digestive, and in 185 cases there was no case of mesenteric lymph-gland involvement as the only tuberculous lesion in the body."

Medin[5] in 595 autopsies on tuberculous infants under one year found only 6 cases of primary intestinal tuberculosis, while 273 involved the lungs and bronchial nodes alone.

Comby[9] in 1432 autopsies on children found tuberculosis in 529 cases, the peribronchial glands being constantly involved. He claims that these glands represent the aërial port of entry of the Koch bacillus. He has never observed primary tuberculosis of the intestines.

White and Carpenter reporting their experience in the Children's Hospital in Philadelphia on pulmonary cavities in infants, state "in infants dying of tuberculosis the lungs were involved in 100

per cent. of the cases." Osler quotes the New York Foundling Hospital statistics where in 125 autopsies the bronchial glands were tuberculous in every instance.

Shennan[10] in a report of the material of the Royal Edinburgh Hospital for Children of 413 autopsies on tuberculous children says "from the standpoint of dissemination of tuberculosis throughout the body, the thoracic-gland tuberculosis is the more important and common" (as compared to other sources, especially abdominal tuberculosis). "Dissemination had taken place in most cases apparently from caseous lymphatic glands, principally of the mediastinal group." Shennan lays repeated emphasis on this mode of dissemination and on the fact that these glands are involved frequently without tuberculosis of the lungs (33 in 281 cases).

These figures which represent the most recent studies of widely scattered observers make it clear that we must abandon the earlier idea of the relatively infrequent involvement of the lungs and respiratory tract in children, and must recognize absolutely that primary bronchial and tracheal-gland infection is the rule in tuberculosis in childhood.

1. (*b*) The autopsy records of the Massachusetts General Hospital[17] give fairly complete data regarding obsolete tuberculosis, and in tabulating the 3000 records by hundreds and striking an average where for certain periods no mention is made of glands, it develops that, as far as mention of tuberculosis goes—

	Times
Lungs alone were involved	156
Bronchial glands alone	600
Mesenteric glands alone	69
Bowel alone	5

It is obvious that absolute data could only be obtained where in making the autopsies special reference to this point was made. However, the point is clear enough that upon macroscopic examination the glands are involved alone about four times more frequently than the lung. If one considers the point emphasized by Rabinowitch's[16] review of the literature on latent infection of the glands determined by animal inoculation, it is probable that the relation of primary tracheobronchial gland tuberculosis to primary lung tuberculosis would be nearer 8 to 1.

2. *Evidence of Primary Involvement of Glands, Particularly of Thorax in Animals.* The Bureau of Animal Industry, Washington, D. C., reports[15] that on consulting the files of postmortem records, which are filled at the close of each day's work at all abattoirs having federal inspection, it developed that of 1237 tuberculous cattle, 155 were affected in the cervical glands only, 533 in cervical and thoracic glands only, 124 in cervical and thoracic glands and also in the lungs. The mesenteric glands alone were tuberculous in 4 instances, the mesenteric and thoracic glands in 115 cases, and there were 306 cases of generalized tuberculosis.

These reports of tuberculous cattle were from various parts of the country, being compiled from the records in cities in six different states. They do not indicate that the lungs are ever involved alone and they make it plain that the thoracic glands are involved about five times more frequently than the lungs.

D. E. Salmon, in Bulletin 38 of the Bureau of Animal Industry, 1906, on page 17, says: "It was formerly believed that the lungs were affected in nearly every case of tuberculosis, but more careful studies have shown that the glands of the chest and neck are even more frequently affected than the lungs. From the very careful autopsies made on the animals of the Soldiers' Home, Washington, D. C., 1893, by Dr. Theobald Smith, at that time pathologist of the Bureau of Animal Industry, the following interesting information as to the parts affected was obtained:

Retropharyngeal glands only	9.4
Bronchial glands only	9.4
Mediastinal glands only	9.4
Thoracic glands but not the lungs	50.9
Lungs	37.5
Lungs but not the thoracic glands	1.9
Thoracic organs only	49.1
Total thoracic organs	88.7
Abdominal organs only	1.9
Total retropharyngeal glands	17.0
Total digestive tract, including head glands	59.1
Intestinal walls	1.9
Mesenteric glands	30.2
Portal glands	18.8
Mesenteric and not portal glands	18.8
Portal and not mesenteric glands	7.5
Parenchyma of liver	3.8
Serous membranes	3.8
Glands of udder	1.9

"This table shows the great frequency with which the tuberculous lesions are found in the lungs. If we add the cases in which the thoracic glands but not the lungs are affected (50.9 per cent.) to those in which the retropharyngeal glands only were affected (9.4 per cent.), we find that 60 per cent. of the cases had these glands, and not the lungs, affected. It is very seldom that the lungs are affected without the thoracic glands being also diseased."

Ryder,[13] in charge of the Boston station of the Bureau, has made a careful postmortem examination of 59,460 hogs, of which number 50 carcasses showed lesions of the mesenteric glands only. Of far more frequent occurrence are lesions of the gastrohepatic glands and of the bronchial glands. "In fact our study of the lesions of hog tuberculosis shows that next in the order of frequency to the submaxillary gland infection comes the combination of the submaxillary with the bronchial glands, then the submaxillary bronchial and gastrohepatic glands, next the submaxillary bronchial and gastrohepatic glands, and the liver."

In a certain small number of cases infection probably occurs directly through the respiratory tract, but these instances are extremely rare.

"The disease in hogs is essentially produced by ingestion, therefore the glands and tissues associated with the digestive tract are the most frequent seats of infection. Indeed, the superior cervical glands (in almost all cases the submaxillary gland) are nearly always affected, as at the postmortem examinations held by the bureau inspectors over a consecutive period on 120,000 hog carcasses, 93.3 per cent. were found to contain lesions in these glands. The large tonsils and the large number of lymph sinuses in the lymph glands probably account for the frequency. *Next in importance are the bronchial glands, of which* 27.2 *per cent. were diseased*, while the gastrohepatic chain of glands was involved in 21.6 per cent. of the cases. In all these cases the lesions may involve the entire lymph structure, or only the central or several irregular points, and may be either caseous, calcareous, or caseocalcareous. The mesenteric lymph glands showed lesions in 18.1 per cent. of the carcasses examined. The liver was affected in 9.2 per cent. of the cases. The lungs are the next tissue to be most frequently affected,

as it is represented by 7 per cent. of the carcasses above recorded. The morbid anatomy of the lungs in this disease simulates that observed in human tuberculosis more than in cattle tuberculosis. In fact, the disease bears many points of similarity to infantile tuberculosis in the human. There may be tuberculous pneumonia involving large areas of the lungs, causing collapse of the marginal portion. There may be irregular sized grayish or yellowish areas of caseation, as is so often seen in cattle, but not infrequently there are observed large areas of miliary gray or translucent foci, showing evidence of generalization as a result of the bacilli being disseminated by the blood stream."

The chief point in these abstracts from Ryder's article is that the lungs are involved in 7 per cent. of cases, whereas the bronchial glands are involved in 27.2 per cent. The fact that 93 per cent. of hogs show tuberculous lesions in the cervical and submaxillary glands is exceedingly interesting, especially in connection with the average of 20 per cent. involvement of the gastrohepatic and mesenteric glands. It seems an argument for the filtering-out process of tubercle bacilli in the upper respiratory and digestive tracts and possibly for germicidal action of the digestive fluid.

It is hard to determine whether the submaxillary and cervical glands suffer in this case as a result of the exposure of the mouth to contaminated food, since the hog bolts its food so rapidly, or because of the exposure of the respiratory tract in the animals rooting around in dust and dirt in search of food.

It is thus shown conclusively in childhood, in adult life, and in the animals most commonly afflicted with tuberculosis, that the usual primary lesions are in the chest glands and not in the lung. This being the case, what is the connection between tuberculosis of these glands and lung tuberculosis? To deny direct aërogenous infection of lung tissue and subsequent extension along lymphatics or bronchi is not at all suggested. Early lung lesions, however, do not indicate that this is the commonest way, but rather that there is a retrograde infection along the lymphatics from tubercular disease of the root glands.

3. *Evidence from X-ray examinations of Extension of Lung Tuberculosis from Hilus Glands.* The evidence presented by

instantaneous *x*-ray plates suggests exactly what is shown at autopsy in children and in the obsolete tuberculosis in adults—namely, that enlarged glands in the hilus are vastly more common than supposed, and in the absence of physical and *x*-ray signs of *lung* tuberculosis, this condition must account for the relative frequency of skin and subcutaneous tuberculin reactions. Indeed, it is a common condition in children and adults with positive tuberculin reactions and negative findings to auscultation and percussion that the hilus glands are found involved on *x*-ray examination. It may be suggested that the subsequent or concurrent lung involvement is due to independent direct aërogenous lung infection, but in answer to this the lung in that case would not be involved so constantly in the direct path of what the *x*-ray shows to be the infection extending outward along the lymphatics.

3. (*a*) The *x*-ray plates made by Dr. Anna Davenport of all the applicants for admission to Arequipa Sanatorium for early cases of tuberculosis in women, together with a number of private cases in women, were made a basis for the study of hilus gland tuberculosis and its possible relation to the lung process. In a series of over 200 plates of early cases about one-half presented striking evidence of a V-shaped segment of lung in which the linear markings were thicker than elsewhere in the lung and were described as mottled, nodular, or beaded. The distal portion showed diffusely increased shadow in some cases or definite more or less plain nodes, often in groups, but sometimes single. Occasionally such nodes, more marked than the beaded appearance, occurred somewhere between the hilus and the periphery, emphasizing the greater development of the process at those points as it extended. But most significant was the frequent occurrence of nodular outlines in the hilus of the affected side and generally in that part of the hilus from which the thickened linear markings emerged. From these hilus nodules, extending toward the periphery at short intervals or apparently in chains, were progressively smaller nodules, suggesting nothing more plainly than direct extension outward. In a few cases large mediastinal glands could be seen protruding their shadows from that cast by spinal column and sternum. In one such case an abscess of the root extending outward from a group of very large

glands, seemed due to the breaking down of one gland and the dense V-shaped shadow extending out from the root to the axilla suggested a tuberculous pneumonia from acute and intense diffusion, such as might have occurred had one of the larger secondary bronchi been invaded by the abscess discharge. The clinical signs were insignificant at first compared to the *x*-ray picture but increased rapidly in intensity as the periphery of the lung was invaded. Localized miliary tuberculosis and processes which we describe as tuberculous pneumonias probably all arise in this way. General miliary tuberculosis, of course, arises through the blood stream, but when it is localized in one lobe or part of one lobe it is always a segment with its apex at the hilus and it cannot well be accounted for in any other way than by extension along a bronchus or rupture into an efferent bloodvessel. But bronchial and bloodvessel extensions are not the common method of spread of the disease in the early stages, for we find in early cases far more frequently the hilus glands enlarged and a beaded chain of glands smaller as they extend outward and connected by thickened shadows of the bronchial tree.

Argument against extension in the reverse direction of the lymph stream does not seem to stand in face of the repeated instances of infection against definite currents; for example, ascending infection of the pelvis of the kidney, pleuritis at the right base behind in acute appendicitis, and local pleuritis peripheral to a lung cavity where there is macroscopically healthy lung between cavity and pleura.

So much detail is lost in reproducing *x*-ray plates for illustration that I have omitted them. To illustrate diagrammatically as Ghon[7] has done is not to strengthen the case, since my observations are exactly the opposite of his, nor in contending for the primary involvement of the lung and secondary glands does he explain why these very glands in children, in obsolete tuberculosis in adults, and in animals are involved four to six times more frequently than are the lungs.

3. (*b*) Fifteen children of known tuberculous parentage reacting to skin tests but with no other definite signs of lung tuberculosis were *x*-rayed, and in every one there were enlarged hilus glands

in distinct contrast to sixteen children in the same families who showed neither hilus glands nor skin reaction.

Both of these groups seem very important, for they indicate a marked dependence of the clinicians on the *x*-ray findings in doubtful cases and a growing appreciation of the possible presence of deep-seated lesions in cases where ordinary lung examinations are negative. That there is a noticeable connection between hilus-gland enlargement and lung shadows is evident by the interpretations of the radiographer; and in conversation with Dr. Holmes, of the *x*-ray department of the Massachusetts General Hospital, he expressed himself positively in two particulars: that the glands are involved first and the extension is outward, and that the extension must very often be along the lymph channels causing the thickening, since neither bloodvessels nor bronchi are thickened in early processes.

3. (*c*) From January 1 to May 1, Drs. Walter Dodd and Holmes (Massachusetts General Hospital *x*-ray department) have made 98 plates of chests of patients suspected clinically of having early pulmonary tuberculosis. The *x*-ray interpretations are as follows:

Lungs definitely involved	46
Doubtful	12
Negative	1
Lungs involved, peribronchial glands enlarged	9
Lungs involved, glands enlarged, markings thickened	12
Lungs involved, glands not mentioned, linear markings noted as thickened or studded	8
Lungs not diagnosed tuberculous but glands enlarged and markings thickened	10
	98

3. (*d*) There were 19 cases on record since January 1, 1913, where involvement of the thoracic glands was in question clinically. The *x*-ray interpretations were as follows:

Lung alone involved	0
Glands alone involved	8
Glands and thickened markings	4
Glands and lungs involved and thickened	7
	19

Jordan,[18] radiographer of Guy's Hospital, reported recently on the *x*-ray findings of 150 consecutive plates of cases of

clinically positive tuberculosis with bacilli in the sputum. The *x*-ray showed:

Purely apical tuberculosis	32
Confined to roots	59
Apex and root on one or both sides	59
	150

After quoting Allbutt as saying that intital lesions occur most frequently below the extreme apex, he adds, "more frequently by far the disease commences at the roots and extends along the branchings of the large bronchial tubes."

Occasionally in obsolete tuberculosis of the lung a healed nodule is found in the lung substance showing no connection with the hilus glands which may or may not be enlarged. Whether these are primary cases of air-borne infection one can only surmise. They are not common and not easily accounted for.

The extension of the studded and thickened linear markings to all the definite peripheral lesions in a given case, and even to areas adjacent to seats of definite lung involvement, suggests constantly efferent and not afferent spread of infection, in the latter case the markings would show from the obvious lesions to the hilus glands only. This is not the case, however, for the markings with the nodular thickenings frequently proceed to no definite lesions, and where they do so proceed they seem to be disseminated to neighboring parts as well. Frequently the most peripheral early lesions are the most advanced, but in every such case it is a matter of note that the lesions are just below the pleura as if the bacilli had been carried along the lymphatics rapidly as far as they could be, and there had made their stand.

4. *Experimental Dissemination.* Of the light thrown on the subject of modes of entrance and dissemination of tubercle bacilli in the human body through experiments on animals, not much can be said.

An ascending infection of the lungs from lesions in the bowel and mesenteric glands was suggested by von Behring and the case was well presented by Harbitz,[11] who reviewed the literature on this subject and established the point. Tracing out the course of

the infection has been tried by the injection of various pigments, chiefly blue, china black, and cochineal, into the gut or peritoneum. No very striking results have been obtained. Calmette[19] found results of peritoneal injections of insoluble substances in young animals always negative, and so many old animals have acquired a lung anthracosis that results are not easily interpreted. Mace[20] tried talc and recovered it by chemical test, but got negative results.

Bacilli have been fed to animals even through a tube and have been introduced into the stomachs of animals through operative wounds, but no results of the details of the spread have been obtained. Ravenel showed that the bacilli did reach the lung. Even a few hours after injection or feeding live bacilli to rabbits he removed the lungs, macerated them and injected a part into animals thereby producing a tuberculosis. This does not show us how the extension goes on. It is obvious, however, that if the lungs are infected rapidly, the infection must spread directly through normal channels of lymphatics and reach the circulation.

To meet the problems involved a number of experiments were undertaken on rabbits into whom were injected dried dead tubercle bacilli stained with carbol-fuchsin, and washed in weak acid alcohol and repeatedly in salt solution and then ground up as fine as possible in a mortar. They showed a decided tendency to clump, and grinding was necessary on that account.

Injections were made into the lateral ear vein in order to show the type of lesions that would be made in the lung, then into the region of the cervical glands, the right foreleg, and the peritoneal cavity. Injections were repeated daily for four days.

The results of the experiments will be reported in detail later. So far they promise to mark out certain channels very well, but the tendency to local abscess formation is a serious handicap. Less frequent and less massive injections promise better results.

Conclusions. In man and commonly susceptible animals the tracheobronchial and hilus glands are the commonest seat of definite tuberculosis.

They are involved about four times more commonly than the lungs.

This fact fits in with evidence of *x*-ray plates in early cases of extension outward:

(*a*) Through rupture of caseous glands into a bronchus, causing caseous tuberculous bronchopneumonia;

(*b*) Through efferent bloodvessels causing localized miliary lesions;

(*c*) Through rupture of or extension from caseous glands into lymphatics making the common type of mild local lesions which, like aërogenous infection of lung tissue, respond relatively easily to treatment.

Ascending infection from abdominal lesions plays a definite but small role.

Animal experiments on mode of diffusion of tubercle bacilli or inert substances are not yet satisfactory.

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DISCUSSION

Dr. Theobald Smith: An observation from a study of spontaneous tuberculosis in animals may be of interest in this connection. Twenty years ago studies showed that in animals the primary tuberculous infection is always in the lymphatics, whether of the chest or of the abdomen.

There is one central gland in the thorax which is most often infected and probably always by inspiratory infection; secondary infection from this gland is by the blood stream. I do not remember but one case in which there was any evidence of a retrograde infection of the lungs from the glands.

In cattle there is no relation between cervical gland infection and lung infection.

Dr. Brown: I wish to ask Dr. Smith if secondary infection from the central thoracic gland referred to is always by the blood stream, how does he account for local lung infection in such cases?

Dr. Smith: The gland referred to in cattle drains the large lobes of the lungs and is most often infected; when infected material escapes from the gland into the blood stream, miliary tuberculosis, of course, results. When local lung infection occurs together with infection of this gland, it is assumed that the lung invasion is the result of a second new infection, from without.

A CASE OF RECURRENT PNEUMONIA

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AND
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MONTREAL, CANADA

The patient whose lungs have been so frequently the seat of acute pneumonia is now a girl, aged fifteen years. She has always lived in Montreal. Her father is an alcoholic, and her mother has recently been under treatment for tertiary syphilis. One of this family died in convulsions within the first year and another was still-born. The patient has been subject to infections of various kinds. Her history shows that by the time she was five years of age she had suffered from measles, bronchitis, and whooping cough. To this list may be added four attacks of chorea, and when first under my care in 1909, well-marked signs of mitral stenosis were present.

From the history we learn also that the patient had pneumonia at the age of five. The second and subsequent attacks of pneumonia have been observed in the Royal Victoria Hospital during the last four years. There is scant history of her case from the age of five to eleven beyond that of recurring chorea with endocarditis.

When first seen with pulmonary signs in July, 1909, her appearance was that of a child below the average intelligence. She was poorly nourished, a mouth breather, with poor teeth, and a high, arched palate. The highest temperature in this attack, which lasted four days, was 103.6°, ending by crisis. The signs were confined to the left base, and while not outspokenly those of consolidation, the case picture was that of a pneumococcic infection.

In April, 1910, she returned to the ward on the fifth day of an attack which set in with headache and chill, and severe pain in the right side of the chest. The signs were those of consolidation

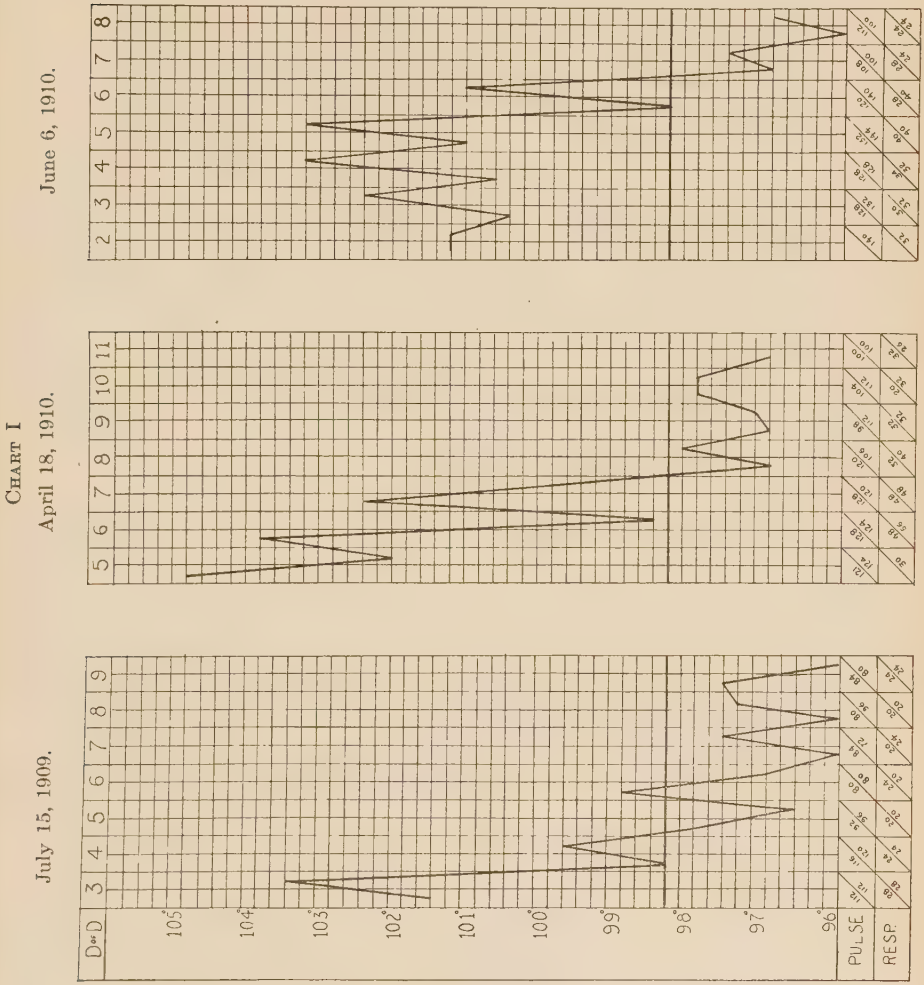


CHART I

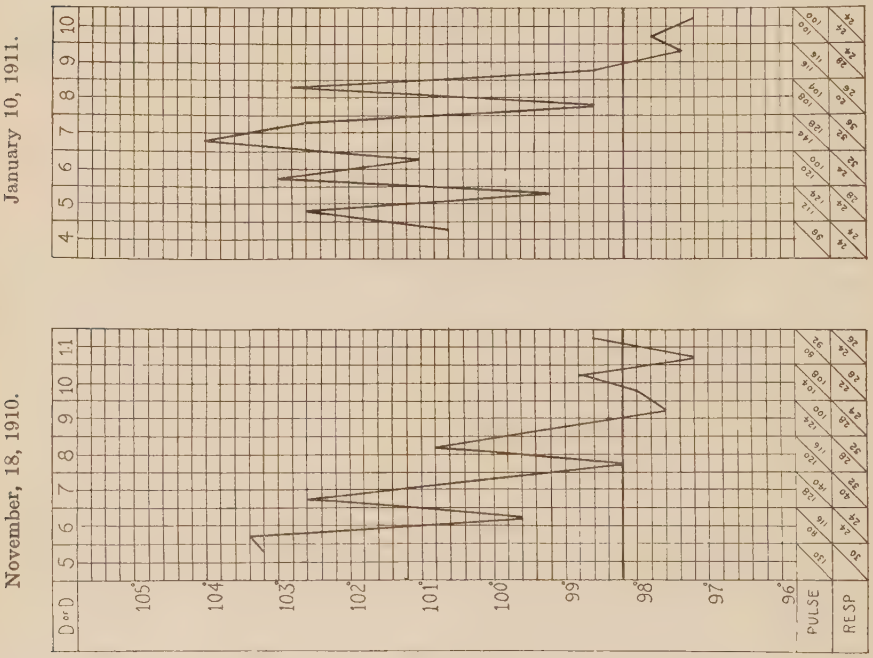
at the right base with a high (105°) temperature, rapid (124) pulse, and just before the crisis, rapid (56) respirations.

The fourth attack found her again in the hospital on June 6, 1910, with the left base involved. The crisis occurred on the

seventh day. In November of the same year a fifth seizure was experienced and the right base was implicated with some suspicion of the right apex also. The temperature of 104° fell by crisis on the ninth day.

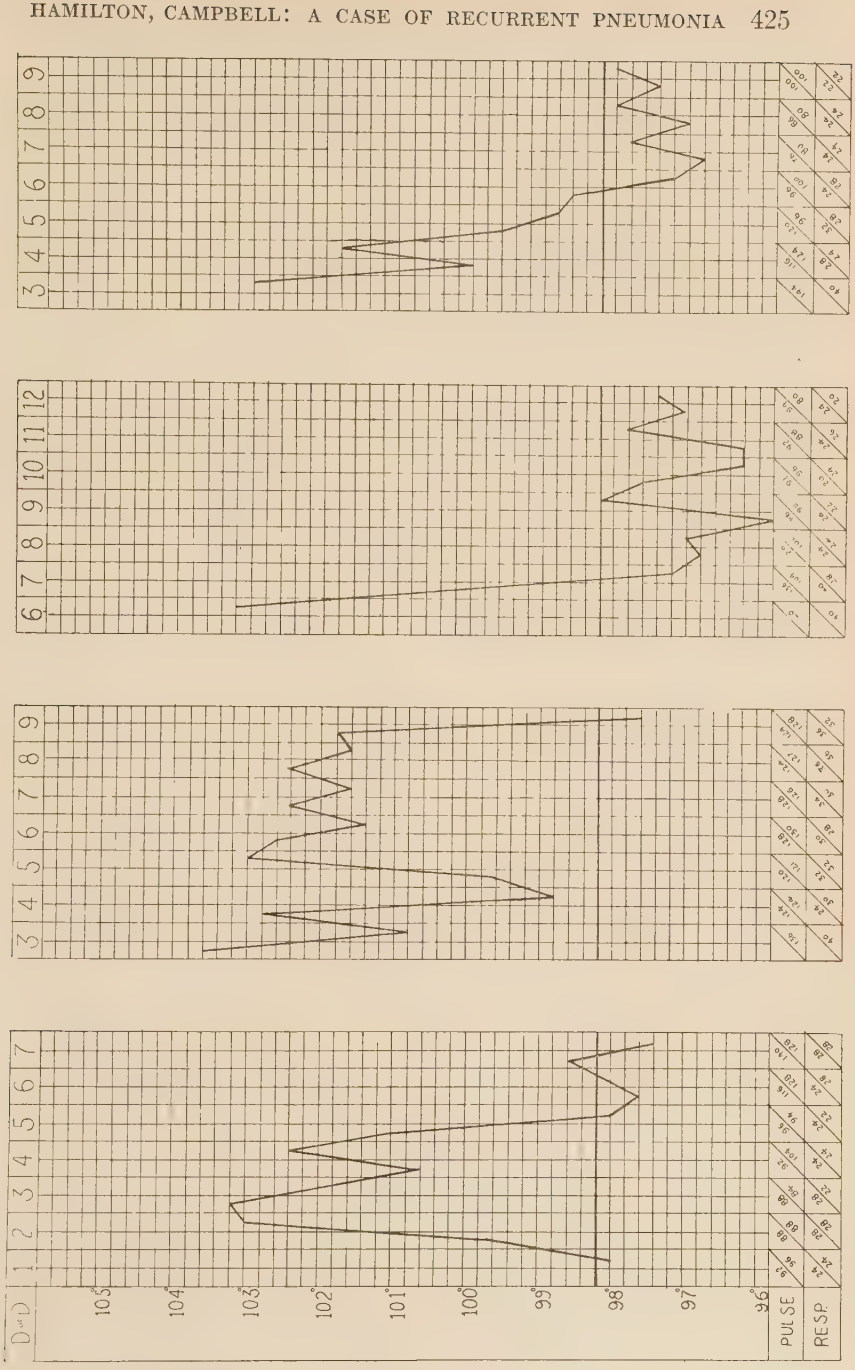
In a little more than four weeks from the time she was discharged the patient complained of pain in the right shoulder, chilly sensations, and fever. She walked into the hospital on January 10, 1911, and presented again the signs of right lower lobe consoli-

CHART II



dation and on the ninth day the temperature fell by crisis. This ended the sixth attack, and on February 5, while yet in the hospital, the fever recurred. There were well-marked signs of consolidation at the left lower lobe. The white-cell count was 20,000, and a pure culture of pneumococci was obtained from the blood. On the third day of the seizure the temperature fell by crisis and two weeks later the patient was discharged in good condition. After the seventh experience of pneumonia, a period of several months elapsed

CHART III


January 10, 1911.
July 24, 1911.
September 29, 1911.
December 4, 1911.
Day of Disease
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
PULSE
RESP

before the next recurrence. It was July 23 when all the symptoms returned with signs in the left lower lobe; high leukocytosis, 32,000; high temperature; rapid respirations, and lysis on the ninth day.

In the ninth attack in September, 1911, the middle lobe and part of the right lower lobe were involved, the temperature again falling by crisis on the seventh day.

The admission on December 4, 1911, was for treatment of the tenth attack, which seemed to have been brought on by exposure to cold on December 2. The alternation of the lesion with each subsequent illness was again borne out and the left lower lobe, both by physical signs and a shadow picture, was shown to be the part now involved. The temperature fell by lysis on the sixth day.

The eleventh attack set in on February 27, 1912. The case picture was very much as others had been. The right base was consolidated. The leukocytes reached the highest so far, numbering 48,600.

The next attack was in April, 1912. The left base was involved. The sputum was blood-streaked. There was delirium. The crisis came on the fourth day. The signs cleared promptly and the patient after ten days of normal temperature was discharged well.

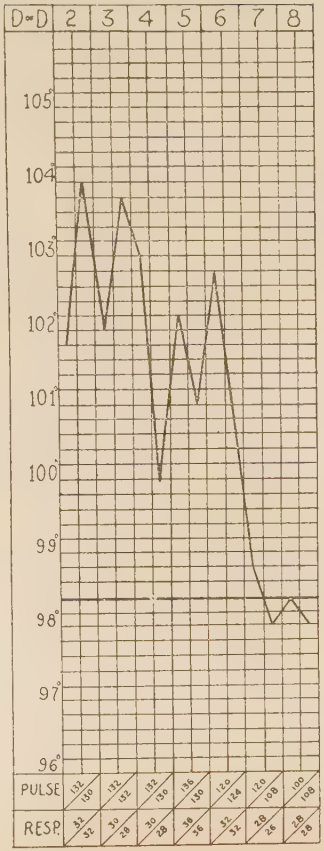
On May 15 the thirteenth seizure set in. The right lung was attacked. The signs were distinct. The white cells numbered 48,400. The fever fell by crisis on the fifth day and remained below or about normal until the patient was discharged on May 28.

The last attack (the fourteenth) up to the time of writing began on November 28, 1912, with chill, pain in the left side, cough, and bloody sputum. In addition to the typical thoracic signs of pneumonia of the left lower lobe, albuminuria was present with hyaline and granular casts. The white cell count was 36,000. The fever terminated by crisis on the fifth day, and the signs of consolidation cleared up as satisfactorily as after all previous attacks.

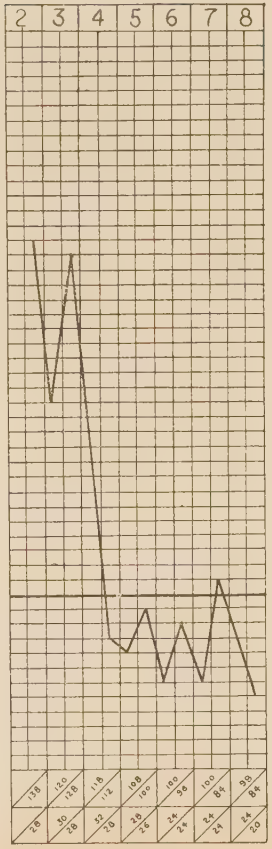
The patient was seen at her home on May 2, 1913. She looked quite well, yet still subject to cough. No illness was experienced since the attack in November, 1912.

CHART IV

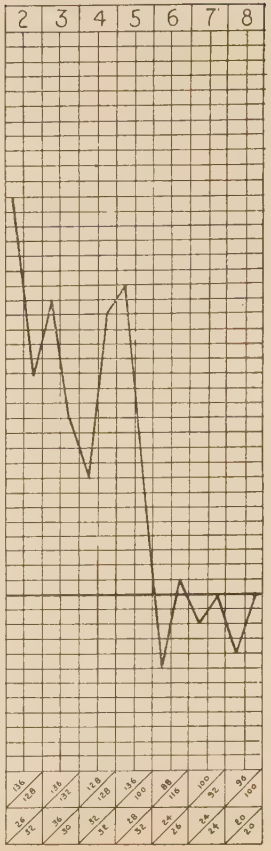
February 28, 1912.



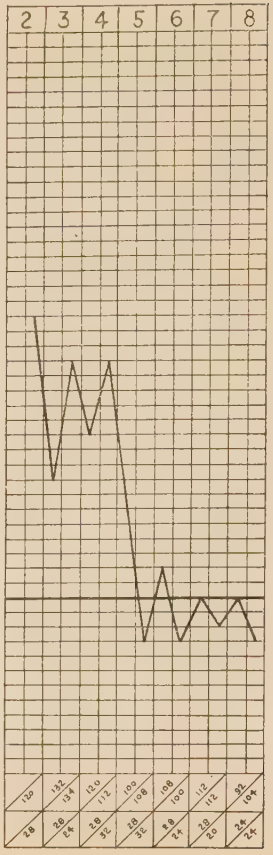
April 8, 1912.



May 12, 1912.



November 28, 1912.



While it is recognized that "recurrence is more common in pneumonia than in any other disease," yet there are certain features of this case which prompted this report. According to the literature fourteen attacks have been exceeded in several instances, yet few patients of this child's age have had so many seizures. The duration of the attack has been from three to nine days and the period of convalescence has been brief and very satisfactory.

While the initial chill has been comparatively rare, the temperature has terminated by crisis in most attacks, and throughout convalescence it has remained normal or subnormal.

The right and left lower lobes have been involved about an equal number of times, and it is of interest to note the alternation.

The shortest period between attacks was that between the sixth and seventh attacks, from January 15 to February 5, twenty-one days.

While under observation from time to time tests for tuberculosis and syphilis have been applied. On one occasion von Pirquet's test was regarded as positive. On two subsequent trials, however, it was quite negative, and tuberculin subcutaneously injected was also negative. The sputum examined frequently contained no tubercle bacilli, while the Wassermann test failed to show syphilis even with so suggestive an appearance and history.

There is in this patient a permanent shadow over part of the left lower lobe as shown by the fluoroscope and radiogram. While signs of acute disease have been found here as already described, there remains a shadow as of a lung with fibrosis. The signs, the early illnesses, and chronic cough are suggestive of bronchiectasis. Is it reasonable to regard this area as a source of recurring pulmonary infection? When judged by the course of undoubted cases of bronchiectasis, however, this view is not upheld.

When one excludes pulmonary infarcts as an explanation of these recurring attacks—and this is done without difficulty, although the condition of the heart suggests infarction—the diagnosis of recurrent pneumonia is easily made. The onset, the course, the signs, the termination, the well-being between seizures, cannot be otherwise explained. It is not a recrudescence of the disease.

The illnesses cannot be classified as relapses. They are distinct attacks—recurrences.

Attack.	Chill.	Duration.	Crisis day.	Side.	Blood in sputum.	Remarks.	Date of onset.
1.	At age of five no records of which are available.						
2	Chilly	4 to 5 days	4th +	L.	..	Friction	July 15, 1909
3	+	8 days	8th +	R.	..	22,000 W. C.	April 18, 1910
4	—	..	7th —	L.	..	37,400 W. C.	June 6, 1910
5	..	..	9th —	R.	Blood streak.	Puncture negative Von Pirquet positive	Nov. 18 1910
6	Chilly	..	9th +	R. Apex R. Lower	.. ..	Von Pirquet negative	Jan. 10 1911
7	..	3 days	3rd +	L. L.	..	20,000 pneumococci in blood post.	Feb. 5 1911
8	Chilly	9 days	9th +	L. L.	+	Blood culture negative; Von Pirquet negative	July 24, 1911
9	—	7 days	7th +	R. M. R. L.	—	32,000 29,000	Sept. 28, 1911
10	—	6 days	Lysis, 6th	L. L.	+	Tuberculin negative 30,500	Dec. 4, 1911
11	..	7 days	7th +	R. L.	..	Wassermann negative 48,600 B. C. negative	Feb. 28, 1912
12	Chilly	4 days	4th +	L. L.	+	43,600 B. C. negative	April 7, 1912
13	—	..	5th +	R. L.	+	46,400 no tubercle bacilli.	May 15, 1912
14	+	..	5th +	L. L.	+	Albuminuria.	Nov. 28, 1912

NOTE.—Since the above report was read the patient has passed through another attack almost as typical as those already described. While in the hospital the Wassermann test was found positive.

ON A LOBAR FORM OF BRONCHOPNEUMONIA OF LONG DURATION, OCCURRING IN CHILDREN AND YOUNG ADULTS

By DAVID RIESMAN, M.D.
PHILADELPHIA

For some time, possibly four or five years, I have been interested in a disease of the lungs which cannot be readily classified nor easily named. The first case I saw was in a young girl who came to the dispensary of the Polyclinic Hospital and puzzled my colleagues and myself by a long-continued, low fever. Week after week on her visits to the clinic we noted a moderate elevation of temperature, and as she had a cough, was pale and of poor physique, tuberculosis was naturally suspected. But aside from failure to find any evidence in the sputum, the physical signs—an abundance of crackling rales—were strictly limited to one lower lobe, there being no involvement of the apices. The history did not suggest an unresolving lobar pneumonia, and the child so far as I can recall —the record is now lost—was not confined to bed at any time. After a most protracted course, covering possibly two or three months, the girl recovered completely.

On September 12, 1911, I saw in my office Pearl L., a girl, aged thirteen years, who had been coughing for two weeks. At the age of two she had whooping cough, otherwise she had been well. Although she did not appear to be very ill, I found impairment of resonance over the entire left lower lobe and sharply limited to it. The breath-sounds were harsh and of a bronchovesicular character. There were also numerous crackling rales. The right side, as well as the upper lobe, of the left lung was entirely normal. The temperature was 99.5°, the pulse 120. Four days later the signs

were more marked, the involvement extending from the base of the left lobe to a little above the middle of the left scapula and over the spinal column to the postaxillary line. The impairment was, however, very slight and only discoverable by careful comparison of the two sides. The rales were of a coarse, moist type; the temperature was 98.9°, the pulse 108. On her next two visits very few rales could be detected. On October 27, six weeks after I first saw her and eight weeks after the beginning of her illness, coarse rales confined entirely to the left lower lobe could still be heard. On November 22, no rales could be found, but as late as January 4, 1912, four months or more after the onset of the disease, the breath-sounds over the left base were still a little harsh. I saw the girl again February 17, 1912, for some trifling condition, and at that time the lungs were clear.

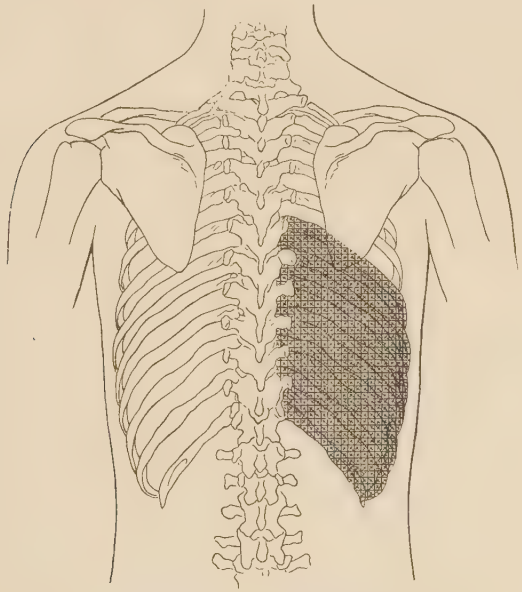


FIG. 1.—Bertha M. Impairment of resonance; bronchovesicular breathing; crackling rales; right lower lobe.

CASE 3. Bertha M., aged nineteen years, a Normal School girl, born in Philadelphia, came to see me March 31, 1911, on account of a severe cough from which she had suffered on and off for three

months. She is very robust and comes of healthy stock. The cough had "somewhat run her down," to use her own words. The temperature was 100.5°, the pulse, 120. On examination I found impairment of resonance over the right chest from the angle of the scapula to the base. Over this area the vocal fremitus was a little increased. On auscultation over the entire lower right lobe posteriorly, laterally, and in front from the mammary region down, numerous crackling rales could be heard. The lung elsewhere was normal. The patient had no expectoration; the appetite was diminished; the bowels constipated. By April 8, only a few dry rales remained at the base of the right chest.

Case 4. Bernice B., aged six years, had whooping cough soon after birth, a mastoid operation and adenectomy at three, otherwise nothing except slight anemia and transient choreiform movements. I saw her first on May 28, 1912. She had been coughing for some time. On June 6, I noted in my records: Cough very hard, temperature, 99.4°, harsh breathing at left base. On June 10: Cough continues, temperature, 99.4, slight impairment of the percussion note over the left lower lobe posteriorly and in the axillary region, with harsh breathing and a fair number of fine rales. One June 17, the notes state: Temperature normal, cough less severe, rales have nearly all disappeared.

Case 5. Dora Y., aged thirteen years, seen with Dr. Hofkin on June 27, 1912, the history being that she had been ill with a continued fever for some time; just how long I could yot ascertain. Typhoid fever and afterward tuberculosis had been suspected. There was no cough; no expectoration; the fever was moderate; and at no time had the child seemed very ill. A few weeks before she was taken sick an uncle had died in the same house of lobar pneumonia. Examination of the patient, who was up and about, showed slight impairment of resonance over the entire lower right lobe posteriorly and in the axillary region. The vocal fremitus was not altered. On auscultation a tremendous shower of crackling rales, which became a little finer after coughing, could be heard. Inspiration was harsh and expiration somewhat prolonged, but not bronchial. I ventured the positive statement that the child did not have tuberculosis and would recover fully. In September

Dr. Hofkin wrote to me that the girl had been taken to Atlantic City and that he had found the lungs clear five weeks after our consultation but had noted the persistence of harsh breathing over the formerly affected lobe. When he reëxamined her in September not the slightest abnormality could be detected.

Case 6. Sarah R., aged twelve years, born in Philadelphia, was first seen October 20, 1912. For three or four weeks she had had a severe cough with some expectoration. According to the

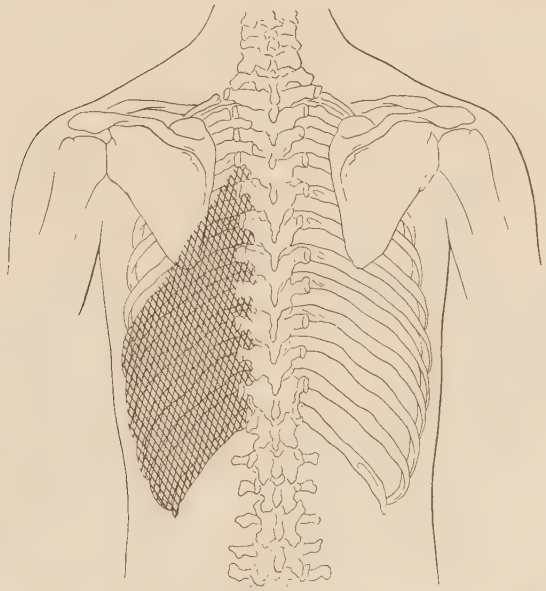


Fig. 2.—Sarah R. Impairment of resonance; bronchovesicular breathing; crackling rales; left lower lobe. Posterior view.

mother the child had been subject to such attacks for several winters, and when once started they would last throughout the cold season. The cough was worse at night and often disturbed the child's sleep. There were no night sweats. The family history was good, and as for the patient, aside from the winter cough, she had had nothing except chickenpox at the age of two years.

Examination showed over the left lung posteriorly a slight impairment of resonance. On auscultation numerous dry and some

moist rales could be heard over the lower lobe of the left lung, behind and as far forward as the midaxillary region. Nowhere else were any abnormal sounds to be detected. The heart was normal; the spleen not enlarged; temperature, 98°, and pulse, 80. A few days later the patient had a severe stitch in the left side with a catch in breathing. When I saw her on October 27, there was no friction sound. The resonance over the left lower lobe was still a trifle impaired; the rales had disappeared.

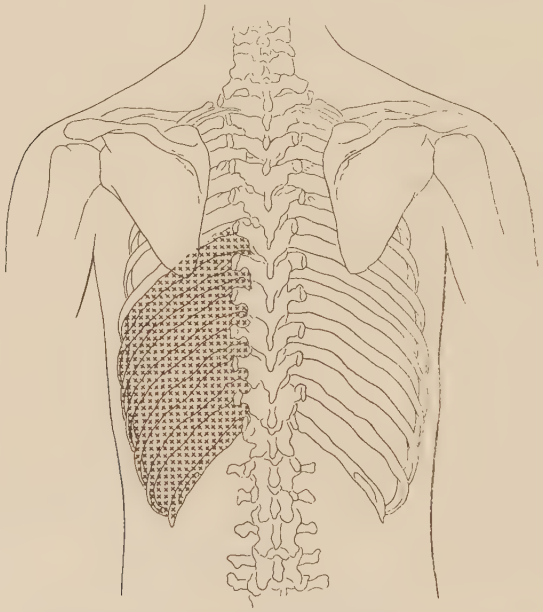


FIG. 3.—W. N. Impairment of resonance; bronchovesicular breathing; crackling rales; left lower lobe.

CASE 7. W. N., a colored lad, aged fourteen years, was sent to me by Dr. Watson at the Polyclinic Hospital on March 1 of this year because just as he was about to undergo an operation for enlarged tonsils it was discovered that he had a little fever. The boy had diphtheria at the age of seven and later frequents attacks of tonsillitis. He did not complain of anything, but after we had detected the physical signs about to be described he admitted that for a week past he had had a slight cough, without expectoration,

and some headache. I wish I could picture to you the surprise of my group of postgraduate students—and my own—when upon examination we found over the left lobe of the left lung many small moist rales, bronchovesicular breathing, and impairment of the percussion note. There was nothing in the history, the symptoms, or in the general impression that the boy made upon as to suggest any trouble in the lung. Had it not been for our prac-

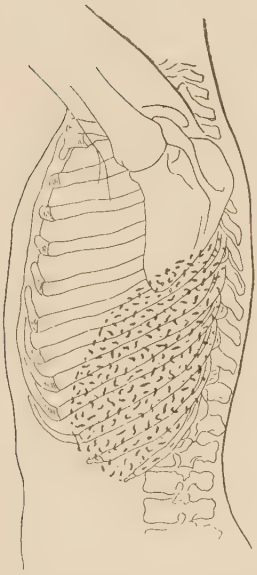


FIG. 4.—Dr. H. Impairment of resonance; bronchovesicular breathing; crackling rales; left lower lobe. Lateral view.

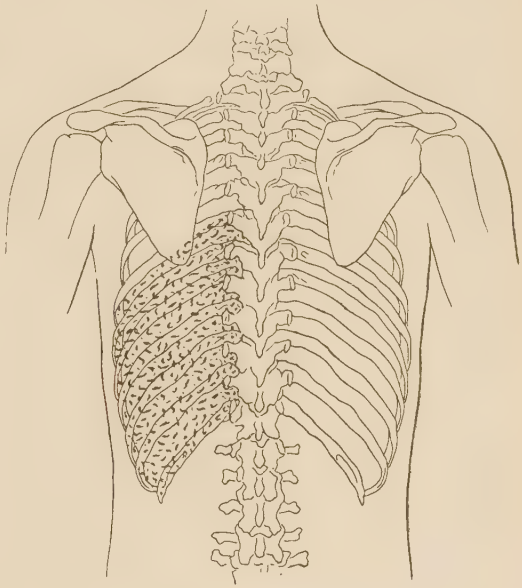


FIG. 5.—Same case as Fig. 4. Posterior view.

tice of making a routine examination of the posterior bases of the lung the trouble would surely have been overlooked. It is not improbable that some of the ether pneumonias are preceded by just such a condition as we found in this boy. If that is true then it behooves us in every case before operation to make a thorough examination of the back of the chest.

The blood count in the boy W. N., gave the following results: Hemoglobin, 88 per cent.; red cells, 5,320,000; leukocytes, 16,160;

Differential count: Polymorphonuclear cells, 57.4; mononuclear cells, 7; small lymphocytes, 28.6; transitional, 5.4, and eosinophiles, 1.6. At the end of three weeks from the time he was first seen the boy was entirely well.

I have cited the foregoing seven cases as typical of the disease. I have seen perhaps double that number.

Pathology. There have been no autopsies and no *x*-ray examinations, so that the actual pathologic anatomy is an inference. The condition is not an ordinary bronchitis: (1) Because it is strictly unilateral, while bronchitis is generally bilateral, and (2) because unlike bronchitis it is accompanied by an impairment of the percussion note and by breathing of a bronchovesicular character. Repeated examination in my cases has shown the physical signs to be quite stationary in the part first affected. Nor can the condition be a pleurisy; the signs remained unchanged, no fluid is demonstrable, the tactile fremitus is either not altered or increased, and the line of dulness follows the slant of the division between the lobes and has not the characteristic curve of an effusion. There is practically no pain.

It is not a lobar pneumonia of the ordinary type, for it has not the acute, sharp onset, nor does one get the impression at any time that there is complete consolidation of the lung. For these reasons also it is not a slowly resolving pneumonia. The view that we are dealing with a lobular or catarrhal pneumonia becoming confluent and assuming a lobar distribution seems to me to accord best with the conditions present. While lobular pneumonia in the vast majority of cases is a bilateral process, there is no inherent reason why it may not be unilateral. As the modes of infection in the two forms of pneumonia are not unlike; and as the infecting organism is generally the same, it is well within the law of probability that lobular pneumonia may be confined to the same part of the lung as lobar pneumonia. Since we possess no satisfactory explanation for the lobar distribution in the one, none can be demanded for a similar distribution in the other.

In some experiments with the pneumococcus, Dr. Kolmer and myself using the Lamar-Meltzer method, produced in dogs a pneumonia confined to a single lobe that to our minds had the

characteristics of a spreading lobular rather than of a true lobar pneumonia, thus bearing a close analogy to the disease under discussion. At best, however, the pathologic differences between lobular pneumonia and lobar pneumonia are neither great nor important.

It has not been possible to obtain sputum in many of the cases. When obtained it showed chiefly pneumococci. The painstaking researches of Luetscher have clearly demonstrated that the pneumococcus is capable of causing not only acute but also chronic pulmonary infections.

There is no evidence that the condition is an interstitial pneumonia of the type so ably described by Dr. Jacobi (*Archives of Pediatrics*, January, 1903), for it heals without residue, without evidence of retraction.

The disease would not impress anyone as a manifestation of influenza. The cases I have seen were scattered over a considerable period of time. They had none of the catarrhal symptoms nor the prostration so characteristic of influenza. Moreover, no other members of the patients' families were affected.

The chief symptoms are cough and a moderate fever, rarely above 101°, extending over a long period—from several weeks to three or four months. The cough may be harassing, but at times is very slight, scarcely of enough moment to attract attention. There may be considerable expectoration or none; it may contain a little blood, but in my experience has never been rust-colored. The physical signs are entirely out of proportion to the symptoms. There is always some dulness, which is best detected by a careful comparison of the two sides, and usually extends to the angle or the middle of the scapula. Rales are as a rule abundant, and of the peculiar quality best described as consonating. They are moist rather than dry, though both types may be found. In the presence of very minor subjective symptoms the listener will be surprised when approaching the base of the chest to find his ear bombarded by a chorus of exquisite crackling sounds. The rales are heard best on inspiration and are often increased by coughing. In the majority of cases the disease involved the lower left lung, but this may be a mere coincidence, as the number of cases is as yet too small for a definite conclusion. Girls predominated among my patients. As

to age, the majority were between ten and twenty, one was twenty-seven and one twenty-eight years. All the cases have ended in recovery without a vestige of the morbid process remaining.

On looking—not exhaustively—through the literature I find nothing of moment directly bearing upon our subject. A number of authors in their chapters on bronchopneumonia state that at times the disease is most marked in one lobe and when confluent may simulate lobar pneumonia. Such types are, however, described as exceptionally severe, with high fever, marked dyspnea, profound prostration, and great danger to life. They differ thus radically from the disease of which I have spoken. Beddard (*System of Medicine*, Allbutt and Rolleston, vol. v) speaks of a primary lobular pneumonia which is usually confluent and diagnosticated as lobar. This, however, has a sudden onset with high temperature and severe nervous symptoms; the duration is shorter, the pyrexia is more regular and sustained, and often ends by crisis. This, of course, does not correspond. West (*Diseases of the Organs of Respiration*, London, 1909) described three types of bronchopneumonia, none of which corresponds to the one under consideration; although he recognized a secondary bronchopneumonia, not, however, of lobar type with a protracted course, lasting three months or more. The nearest approach is found in Powell and Hartley (*Diseases of the Lung*, fifth edition, 1911). They speak of a confluent form involving adjacent lobes of a large portion of the lung, sometimes a whole lobe, producing more or less dense consolidation. It may be associated with ordinary bronchitis of catarrhal origin, and very often occurs in the course of whooping cough. They have also met with it in certain cases of heart disease and as a complication in pulmonary tuberculosis. In none of my cases was whooping cough, heart disease, or pulmonary tuberculosis a factor in the process; moreover, in severity and course the condition described by Powell and Hartley and the one here discussed are very different. Babcock (*Diseases of the Lung*, New York, 1907) recognizes a confluent bronchopneumonia, but does not go into details regarding the symptoms or course.

Treatment. In the treatment the measures that have seemed to me of some avail are counter-irritation to the chest, abundant

feeding, and either a simple cough mixture with a small dose of an opiate, or one of the creosote preparations. Whenever the weather was favorable I advised that the patients be out of doors. A sojourn at the seashore in proper season is also beneficial.

The essential features of the condition I have described may be epitomized as follows:

(*a*) The condition is a confluent lobular pneumonia of lobar distribution characterized by long duration, low fever, and the following physical signs: impairment of resonance, bronchovesicular breathing, and showers of crackling rales.

(*b*) It must be looked upon as one of the causes of obscure long-continued fever.

(*c*) The disease always seems to end in complete recovery, both symptomatically and anatomically.

(*d*) In the beginning typhoid fever may be suspected, in the later stages tuberculosis.

(*e*) The disease is, I believe, often overlooked, due to the fact that we seldom examine the lower posterior aspects of the chest in ambulatory cases, especially when the symptoms are rather trivial. I am quite sure the diagnosis of tuberculosis is often made in these cases of chronic cough, with low, continued fever, but if the chest is carefully examined, back and front, above and below, the peculiar, almost specific character of the disease will be discovered, and then the thought of tuberculosis will be no longer entertained.

DISCUSSION

Dr. R. C. Cabot: Was there an autopsy in any case in Dr. Riesman's series? Were any tapped? In the absence of such proof, how does Dr. Riesman know he was not dealing with pleurisy with a small effusion, or with thickening and no effusion?

Dr. F. T. Lord: The study at autopsy of cases of bronchopneumonia suggests an explanation of the pathology of the cases reported by Dr. Riesman. In some cases small losses of pulmonary substance forming the beginning of abscesses and acting as pockets for the retention of pus and

bacteria may be found. In other instances, with or without the development of such abscesses, an increase of interstitial tissue may be noted in the involved parts. These changes may be classed as subacute or chronic indurative pneumonia. The complete recovery of Dr. Riesman's cases does not, it seems to me, necessarily eliminate them from those with such a pathological picture, inasmuch as losses of pulmonary substance may heal and contraction of scar tissue, together with compensatory emphysema of the neighboring parts of the lung, may so materially diminish the size of the affected region as to make it undetectable on examination.

Dr. Jos. L. Miller: There are not a few such cases as these reported by Dr. Riesman. Such cases are described by Leichtenstern, who formerly thought that they were of influenzal origin, but later found the pneumococcus present in the sputum.

Dr. J. B. Leathes: I have seen only one case similar to Dr. Riesman's cases. Whether the original distribution was lobular or lobar is not known, but a consolidation was present as shown by *x*-rays. This condition persisted for over six months, with showers of rales to be heard over the affected area; the whole illness was afebrile. Sputum examination showed typical pneumococci in pure culture. All the signs finally cleared up without any residue.

Dr. Riesman: There were no autopsies in my series, because the patients all recovered. I would say to Dr. Cabot that there may have been pleurisy to account for the signs; but my reason for believing that the condition described was pneumonic is that there were no changes in the physical signs for weeks or months, and if there was any change in the fremitus it was increased. There were not enough sputum studies to show whether there were any streptococcus cases in the list.

As to tissue losses, there were no evidences of such losses after recovery.

THE UNCERTAINTIES OF THE TREATMENT OF PULMONARY TUBERCULOSIS BY ARTIFICIAL PNEUMOTHORAX: REPORT OF A FATAL CASE, WITH AUTOPSY

By LAWRASON BROWN, M.D.
AND
ALLEN K. KRAUSE, M.D.
SARANAC LAKE, N. Y.

The perusal of a large number of communications upon the treatment of pulmonary tuberculosis by artificial pneumothorax would suggest that the treatment is simple, efficacious, and of slight danger. In many instances, the introduction of nitrogen into the pleural cavity is a simple procedure, but this, unfortunately, is not synonymous with successful treatment by artificial pneumothorax. I want to emphasize some of the errors I have made in the employment of this method and to mention some of the dangers that accompany the treatment as well as, with the aid of Dr. Krause, to report a case which terminated in death.

The untoward results of collapse therapy may be roughly divided into (1) those interfering with the treatment and (2) those threatening life. Of all the complications that interfere with treatment, pleuritic effusion is the most frequent. In about 50 per cent. of the cases it is demonstrable. The cause of this effusion is of much interest on account of its bearing on the treatment. Some claim that tubercle bacilli are always to be found, but I have not been able to demonstrate them in several instances. It is of interest to consider the effect of chilling upon the production of an effusion, especially in a tuberculous patient with a collapsed lung. The amount of heat supplied to the parietal pleura by the lung must be considerable and it is of much interest to picture the

condition of the chest wall after collapse of the lung. Under these circumstances it must depend entirely upon its own circulation to prevent chilling. It might be a wise plan, especially in cold climates, to have the patient provided with a piece of flannel, similar to the flannel abdominal bands, covering the side. He should be warned against exposure to cold and the gas heated during injection. When a marked effusion has occurred, the difficulties of the treatment are increased manyfold. This is especially true where the collapse is only partial. It increases the intrapleural tension; it glues the surfaces of the pleura together so that they quickly become inseparable and, strange to say, the lung in some way seems to expand and to resist renewed efforts at collapse. I have had two cases similar to this, one which has done remarkably well and the other fairly so. Both have partially expanded lungs and still some effusion.

Empyema may in rather rare cases supervene upon an effusion. I have had two instances of this, one of which I will mention later. The other was in a patient who has had pulmonary tuberculosis for sixteen years, who had a slowly progressing disease with extensive involvement of both sides (cavity on the left), and one year ago returned to Saranac Lake expecting to die in a short time. I unfortunately had nothing else to suggest and his left lung was partially collapsed in May, 1911. During the fall, he developed an effusion, which later became purulent, and for some time no organisms were found in the pus, either by culture (aërobic and anaërobic) or by inoculation. Recently a guinea-pig has developed tuberculosis. I now hesitate to introduce the needle to withdraw the pus, for each time the pus seems to be forced by cough along the track of the needle and to form what appears like a cold absces, which occasionally discharges a little and which fills and becomes tense when the patient assumes a sitting posture.

Subcutaneous emphysema rarely causes much discomfort, but when the patient has a violent cough, the intrapleural pressure during coughing must rise nearly to or indeed even above 100 cm. of water. This may force the gas into the subcutaneous or mediastinal tissues or possibly outside the parietal pleura and so into the deep tissues of the neck. Long straps of adhesive firmly applied

may prevent this unpleasant subcutaneous complication, which in none of my cases caused anything more than transient discomfort.

Another difficulty frequently met with is the occurrence of pleuritic adhesions. The degree of negative pressure that is registered when the needle is first inserted into the pleural cavity indicates in a general way the extent of the adhesions, but tells nothing of their tenacity. The negative pressure is due to the elastic recoil of the lung and proportionally as it is exerted upon adhesions it is reduced in that part of the pleural cavity that is free. The percentage of patients suitable for the treatment in whom collapse therapy can be successfully applied is small on account of these adhesions. It ranges, according to various estimates, as low as 4 per cent. In twenty-two patients, I could produce no collapse in eight, a partial collapse in six, and a complete collapse in eight, or roughly speaking, in two-thirds the collapse was at most only partial, while in one third it was complete. Much work has been done to determine the presence or absence of pleuritic adhesions, but the only infallible proof seems to be the introduction of the needle. Partial collapse may be productive of good results.

Dyspnea following injection, may be a very urgent symptom. A patient of mine, a physician, had extensive disease on the left and a few fine scattered rales on the right lung. She was somewhat short of breath and slightly cyanotic, and was really very ill. I was loath to give her the treatment but she insisted and I yielded. My second mistake was to inject at first five to six hundred c.c. of nitrogen, as it entered easily and gave her no discomfort. That night her dyspnea and cyanosis were marked and her pulse raced. Early the next morning I withdrew all the gas I could and she slowly recovered, and later her family wished me to repeat the injection, as they said they all thought it had benefited her. She received no more gas and death occurred two months later.

Pain in the chest from the presence or loosening of adhesions may, in rare instances, be very severe and require morphine. It may not occur until some time after the injection of gas or after a severe attack of coughing.

The complications that threaten life fall into the immediate and the more remote. The immediate complications seem in practically all instances to be due to faulty technique or poor selection of cases. Much has been written of pleural shock, a condition in which the patient grows pale and faint, vomits and at times loses consciousness. It occurs usually as the needle passes through the pleura and can be practically always avoided by careful cocainization.

The introduction of gas into the circulation with the production of gas emboli and sudden death or hemiplegia, practically never occurs when the injection is made under manometric control. A case has been reported, however, where the gas entered probably through the wounded vessels of the chest wall. The patient became unconscious and died in about thirty hours.

The danger of advancement of the disease in the non-collapsed lung is real. This lung should be studied as carefully as possible, but even then it is impossible to say beforehand what effect the extra work will have upon it. During the treatment it should be closely watched and the advantage and disadvantage of continuing the compression weighed. In the two cases resulting fatally, fresh advancing disease was present in one and probably, from the physical examination, in the other.

I have had two deaths among my twenty-four cases. Both had spontaneous pneumothorax of the partially collapsed lung. One, a woman, aged forty years, had bilateral advancing pulmonary tuberculosis. Collapse of the right lung held the process in abeyance for a time, but in a short while the process advanced in the left lung and the injection of gas was discontinued on February 5. On April 2 the patient felt a sharp pain in the right lung, became very dyspneic and cyanotic. A few days later a needle was introduced and the pressure reduced from +10 cm. of water to −3 cm. It rose again in one or two minutes, and although the process was repeated several times it produced no permanent effect upon the intrapleural tension. The patient died two days later with signs of failing circulation. The second case, which I shall report more fully but briefly, was as follows: The patient, a woman, aged twenty-six years, by occupation a singer, with a family and previous

history of little importance, began in March, 1910, to have malaise, followed by cough in July, and tubercle bacilli were found in September, when with a temperature of 102° and a weight of 125 pounds (height 5 feet 3 inches), she was admitted to the Loomis Sanatorium. The disease steadily but slowly progressed and in November, 1911 (the weight was 125 pounds), examination of the lungs showed extensive involvement of the right (cavity formation?) and compensatory with fibroid changes in the left. Tubercle bacilli were constantly present, the urine was normal, and on one examination a few acid-fast organisms were found in the stools. The lung was collapsed in November and resulted in reduced cough and expectoration and a lessened temperature which reached normal in December. The temperature ran up again on several occasions and the weight steadily declined to May, 1912 (108 pounds), when the patient left the Loomis Sanatorium to try the effects of change of environment. At this time the patient presented signs of a partial pneumothorax, the middle part of the lung being apparently adherent to the chest wall. Hippocratic succussion was present at the apex and base. On the left lung a few scattered rales were present. At this time the patient came under my care and was given 150 c.c. nitrogen on June 6. The pressure was left at +20 cm. of water. At intervals of two to four weeks, nitrogen was injected in quantities of 150 to 200 c.c. and the pressure was left usually as high as +18 to +20 cm. of water, for she said this gave her the greatest relief from coughing. It was, I believe, a mistake to leave so high a pressure. On January 4 an injection of 250 c.c. was made (pressure up to +25), and that night the patient complained of sharp pain in the right lung and wheezing. On examination a snoring rhonchus was heard over the whole side with maximum intensity in the fourth interspace, over the lower border of the adherent lung. The temperature rose from about normal to 101° and amphoric breathing replaced the former distant breath sounds. Signs of fluid became more evident, the temperature rose to 104° and on January 26, 200 c.c. of pus were aspirated, which contained large numbers of tubercle bacilli. I attempted to wash out the pleura by the use of two needles, but the patient coughed up the saline solution and I was forced to stop. At this time some family difficulties arose and the

patient went rapidly down hill. She became very cyanotic, the left lung became full of coarse rales, and she died after being comatose for twenty-four hours on February 3.

Dr. Krause performed the autopsy and his report follows:

The left thoracic cavity is dry. The lower half is practically free from adhesions, but the upper half contains many that bind the lung to the thorax, particularly to the left side and back and to the top. The lung fills the cavity.

The right lung is very thoroughly collapsed and lies in the vertebral gutter, flattened against the mediastinum and the back of the thorax. Along the mediastinum it occupies about two-thirds of the length of the thorax in a superior-inferior direction. The right thoracic cavity contains about 500 c.c. of thick, dirty, yellowish fluid. This side is also comparatively free from adhesions in its lower one-half; but in the upper part of the cavity are numerous bands that run from the collapsed lung to the chest wall. These are for the most part very heavy and are stretched taut, and give the appearance of thick finger- and band-like processes that traverse the empty space between the lung and the parieties. They are numerous, and in two or three places where they unite with each other, they form pockets which enclose small amounts of purulent fluid. The collapsed lung and the heavy adhesions are covered with a thick, dirty, yellowish exudate.

The left or uncollapsed lung is voluminous; bluish pink in color, especially in the dependent portions; marked by the tags of adhesions, especially along the outer border on both sides of the interlobar fissure; and shows here and there a small gray tubercle which projects slightly above the surface. Section shows the presence of a diffuse tuberculous process which differ in age in different parts of the lung. It is oldest in the immediate neighborhood of the interlobar fissure where in both lobes there are a number of tubercles of the average size of a pea, opaque, yellow, cheesy, and in several instances showing beginning central excavation. Throughout the remainder of both lobes is a miliary involvement of fine, gray tubercles, that average one to two millimeters in diameter. The lung is remarkably free from extraneous pigment.

Considerable difficulty was experienced in removing the right (collapsed) lung on account of the adhesions, and the upper portion

was torn through in the process. The lung is greatly reduced in size to about 15 cm. from above downward, 6 cm. from side to side, and 4 cm. from front to back. It is represented by a shrunken, tough, leathery piece of tissue, the surface of which shows a yellow, wrinkled, enormously thickened pleura, with dense bands of adhesions attached. All distinction between the lobes is lost. What was originally probably almost the whole of the upper lobe is now a cavity which has been torn into in the removal of the lung. The cavity projects irregularly into the surrounding tissue. Along the outer border of the surface of the lung are two small slit-like holes which communicate with the bottom of the cavity and which are very evidently the points where the pleura was ruptured intra vitam. Section of the lung shows a dense, compact looking tissue of a mottled, reddish black apearance which is traversed everywhere by translucent, grayish lines. The black areas which are everywhere and average 2 to 5 mm. in diameter represent areas of pigmentation. The grayish bands and lines are fibrous tissue which is in great abundance and altogether apart from the area where it represents the scarring of old tuberculous foci. Tubercles are quite numerous. The largest is about 1 cm. in diameter. Most are undergoing organization and many are almost completely healed. Where there are no tubercles the lung retains few traces of its normal appearance. It looks more like very dense liver, marked throughout by fibrous tissue. The bloodvessels and bronchi are pressed close together so that very many may be seen in small compass.

There is no tuberculosis anywhere else in the body except old foci in the bronchial glands. The heart, liver, spleen, and kidneys show cloudy swelling. Otherwise no gross abnormalities are to be noted.

Microscopic Section: Blocks were prepared from a part of the lung which showed practically no gross tuberculosis. Microscopically it is seen that the section is made up almost wholly of granulation tissue. In one or two places the remains of a few flattened alveoli may be seen. There are many microscopic tubercles and in places the giant-cell formation is exquisite. Here and there are fresh, single tubercles in the granulation tissue. Since practically the entire structure of the alveoli has been lost, and nothing

but granulation tissue remains, the question might fairly be raised as to whether the fibrosis is the result of a diffuse tuberculosis or of the chronic atalectasis. The gross appearance of the lung together with the microscopic appearance of fresh tubercles in the granulation tissue, make it appear that the induration is consequent to the atelectasis.

DISCUSSION

Dr. F. T. Lord: I have been very much impressed in a review of the cases of spontaneous pneumothorax at the Massachusetts General Hospital by the unfavorable effect which this complication exerts on the course of pulmonary tuberculosis. In such cases it introduces very definite dangers and hastens the fatal termination. The rupture of a small subpleural tubercle, a tuberculous cavity, or a pleural adhesion usually leads to tuberculous or pyogenic infection of the pleura with the formation of a serofibrinous or purulent effusion in consequence of which the fever becomes more marked and emaciation progresses more rapidly. To judge from reported cases, infection of the pleural cavity not infrequently follows the production of artificial pneumothorax. The method seems theoretically unsound because it is assumed that while rest is good for the tuberculous process on the side selected for the procedure, overwork is good for the other and usually already infected lung. These considerations together with the dangers already mentioned by Dr. Brown have thus far deterred me from using the method.

Dr. W. G. MacCallum: What is Dr. Brown's idea as to the cause of improvement attributed to this mode of treatment? Rest and pressure would have obviously good effects upon the diseased lung, but what other factors are engaged? There are so many conflicting ideas among the various modes of treating this disease; some have for their object the increase of activity of the circulation in the lung; some, as this method, probably interfere with the circulation. What effect upon the amount of movement of the collapsed lung does the pneumothorax have? What effect on the local circulation? What effect on the movements of the opposite lung?

Dr. Brown: There has been done no work, so far as I know, to enable one to answer exactly Dr. MacCallum's questions. The diminution of lymphatic drainage from the compressed lung probably has much to do with the improvement noted in cases in which the method has been used. The greatest danger attending the use of the procedure is the liability to hasten the progress of the disease in the opposite lung.

THROMBOSIS AND OCCLUSION OF LYMPHATICS

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The lymph exhibits peculiarities which influence the process of thrombosis within lymphatics. It is well known that the blood platelets have an important part in the formation of white thrombi formed from the circulating blood. Platelets are deposited at the site of an injury which has impaired the endothelial lining of any part of the vascular system, and upon these masses of platelets fibrin is deposited from the plasma of the circulating blood. The lymph contains no platelets, yet it is well known that thrombosis may occur within lymphatics.

Lymph drawn from the thoracic duct of a dog coagulates slowly, the average coagulation time being approximately from ten to twenty minutes, whereas blood from the same dog coagulates within from four to six minutes. Slow coagulation of lymph is doubtless dependent upon the scant quantity of thrombokinase present in the lymph, for the addition of tissue extracts bring about prompt and firm coagulation. This acceleration of coagulation is shown by the following test: 0.5. c.c. of lymph withdrawn from the thoracic duct began to coagulate after thirteen and one-half minutes, but a firm clot was formed only after the lapse of eighteen minutes. The addition of serum obtained from the surface of the wound made to expose the duct brought about such firm coagulation within two and one-half minutes that the coagulum was undisturbed by inversion of the tube.

A number of experiments were performed to test the effect of different tissues upon the coagulation of lymph. The organs of a dog were washed by prolonged perfusion with salt solution injected

into the aorta immediately after death. The tissues were dried on glass plates and subsequently suspended in salt solution when tested. In one series of experiments lymph removed from the thoracic duct clotted loosely in from nine and one-quarter to ten and one-half minutes; the addition of one drop of a suspension of dried spleen brought about coagulation within two and one-half minutes, of lymphatic node, within one and one-half minutes, of brain substance, within one minute, of white substance of brain, within one and one-half minutes.

Equally satisfactory tests can be made with oxalated lymph obtained by dilution of lymph with one-tenth of its volume of a 2 per cent. solution of sodium oxalate. On the addition of calcium chloride (one drop of a 6 per cent. solution) coagulation occurs within a period approximately equal to the coagulation time of unchanged lymph. The addition of calcium to 0.5 c.c. of a specimen of oxalated lymph caused the appearance of clumps of fibrin within fourteen minutes, but a solid invertible jelly was not formed until thirty-four minutes. The addition of one drop of a suspension of dried washed liver produced a firm invertible clot within three and one-half minutes, of kidney within two minutes, and of lymphatic node within two and one-quarter minutes.

It is noteworthy that lymph undergoes spontaneous coagulation, but the clot forms very slowly and addition of tissue extracts brings about firm coagulation, resembling that of drawn blood. The experiments show that lymph has properties similar to those of pericardial or hydrocele fluid, which according to the observations of Alexander Schmidt contain fibrin and fibrin ferment, but is lacking in what Schmidt called fibrinoplastic substance, or according to more recent views, there is thrombin, but thrombokinase is absent or deficient in quantity. The explanation of coagulation of the blood advanced by Howell[1] suggest the possibility that antithrombin if present in the lymph would be found unbalanced by thrombokinase. This suggestion is supported by the following experiment in which pure thrombin prepared by the method of Howell was employed to bring about the coagulation of purified fibrin.

[1] American Jour. of Physiol., 1911, xxix, 187; 1912, xxxi, 1.

0.5 c.c. fibrinogen solution + 2 drops of thrombin + calcium	Coagulation after 10 min.
Same mixture with 1 drop of lymph . .	" " 53 "
Same mixture with 2 drops of lymph . .	" " 33 "

Since the sample of lymph employed coagulated within from nine to ten and three-fourth minutes, it is not improbable that the addition of two drops of lymph introduces factors which tend to counteract the inhibitary influence more prominent in the smaller amount of lymph.

In a series of experiments previously described,[1] edema of the liver and gall-bladder was produced by administration of cantharidin. Lymphatics of the liver were widely dilated. Lymphatics extending from the liver to the regional hepatic lymphatic nodes and the sinuses of these nodes were in many places occluded by fibrin forming a loose or compact net-work. Edema was in part at least referable to obstruction to the flow of lymph. Microscopic examination showed that there was a close relationship between the fibrinous net-work and cells which under the influence of the poison had undergone degeneration. Cells of which the nuclei are pale and ill-defined or wholly lost form centres from which radiate fibrils of fibrin. This relation of fibrin to injured cells suggests the probability that thrombokinase set free by disintegration of cells furnishes conditions favorable to thrombosis within lymphatic channels.

The lack of thrombokinase in lymph and the occurrence of lymphatic thrombosis under conditions which set free thrombokinase within the lymph has suggested that thrombosis might be produced by direct introduction of tissue cells or tissue extracts into lymphatics. To test this possibility the thoracic duct of a dog was ligated near the site at which it enters the venous system, namely, at the junction of the subclavian and internal jugular veins. The abdomen was opened and tissue elements were introduced through a fine needle into a lymphatic near the root of the mesentery. Simple ligation of the thoracic duct, it is well known (Cohnheim[2]), is rarely followed by marked edema or other disturbance. The following experiment shows that simultaneous ligation of the duct

[1] Opie, Journal of Exper. Med., 1912, xvi, 831.
[2] Cohnheim: Volesungen über allegemeine Pathologie, Berlin, 1877.

and injection of cellular elements directly into the lymph is followed by thrombosis within the occluded channel. The thoracic duct of a dog was ligated near its termination. The abdomen was opened and a small lymphatic node was removed from the duodenal mesentery. About 0.1 c.c. of cells and juice scraped from this node was injected through a fine needle into a conspicuous lymphatic vessel situated upon the right surface of the mesentery at its root. Four days later the abdomen was distended and the animal was killed with chloroform. The peritoneal cavity contained 150 c.c. of white chylous fluid; the peritoneal surfaces were injected. The thoracic duct in the thorax was rigidly distended by thrombus material to a diameter of about 4 mm.

Thrombosis of the upper part of the thoracic duct had followed injection of juice and cells from a lymphatic node into the occluded thoracic duct and chylous ascites had followed the operation. It is not improbable that escape of chyle occurred at the site of the punctured lymphatic.

In a similar experiment the animal was killed after eleven days. The upper part of the thoracic duct formed a narrow, irregular cord. It is noteworthy that free lymphatic communication had been established between the lower part of the duct and the uppermost part situated between the ligature and the termination in the vein, so that suspension of India ink injected into an abdominal lymphatic entered the subclavian vein.

In two experiments an attempt has been made to bring about thrombosis of the occluded thoracic duct by injecting extracts containing tissue juices, that is, thrombokinase into the subcutaneous tissues. In one experiment the thoracic duct had undergone thrombosis, following subcutaneous injection of tissue extract. The relation of thrombosis which in the second experiment occurred in a large cervical lymphatic to the subcutaneous injection of extract prepared from the spleen is doubtful, for the thrombosed lymphatic vessel was in immediate contact with the wound made to expose the thoracic duct.

These two experiments demonstrate incidentally the occurrence of edema as the result of complete occlusion of lymphatics. In each experiment a large cervical lymphatic had undergone throm-

bosis and could be traced by dissection to a greatly enlarged lymphatic node. The node and the tissue about it were distended with edema.

Thrombosis of the thoracic duct has usually been absent after ligation of the duct, but it is not improbable that it may occur when the operation has been accompanied by considerable injury to the duct. It may occur when infection of the wound follows operation and has been present in one experiment accompanied by suppuration of the wound and abscess of the mediastinum. In two experiments the condition of the thoracic duct was examined within a short period, namely, two and four days after its ligation. In these and in other experiments no thrombosis of the thoracic duct has followed simple ligation of the duct. They do not exclude the possibility that thrombosis may occur with this condition.

In one of the two experiments just cited, collateral lymphatic circulation had been reëstablished through the right thoracic duct within two days after occlusion of the left thoracic duct. In the second experiment no channels connecting the lymphatic and vascular system were found; in this experiment abdominal lymphatics were dilated and there had been diarrhea. Diarrhea following ligation of the thoracic duct has been found in other experiments and has persisted during a considerable time.

A series of experiments has shown that occlusion of the duct is followed by thrombosis if after ligation bacteria are injected into the circulating blood. These experiments have been suggested by an observation made upon a filarial varix found in a man who had lived in the West Indies.[1] Within the thrombus material in dilated lymphatics were diplococci in abundance and from the varix diplococcus lanceolatus was obtained in pure culture.

The thoracic duct has been exposed by an incision on the left side at the base of the neck and ligated. Bacillus pyocyaneus has been injected through the skin into the right jugular vein. In one experiment bacteria were injected less than one hour after ligation of the lymphatic duct. Thrombosis of the duct was found forty-five minutes later.

[1] Opie, American Journal of the Medical Sciences, September, 1901.

In three experiments Bacillus pyocyaneus was injected into the right jugular vein twenty-four hours after ligation of the thoracic duct. In all three instances there was thrombosis of the upper part of the thoracic duct. In one instance the right thoracic duct as well was occluded by thrombus material.

The absence of edema at autopsy performed from five to ten days after ligation of the thoracic duct is a noteworthy feature of these experiments. In one experiment edema is absent, although the left thoracic duct is ligated and in its upper part occluded by thrombosis, the right thoracic duct being at the same time distended and wholly occluded by thrombus material. Whereas this and several other experiments have shown that occlusion of lymphatics by thrombosis is frequently followed by edema, they have not proved that this is the constant result of complete occlusion of lymphatics. Doubtless rapid establishment of collateral flow through anastomatic lymphatics has a part in preventing edema.

Abscess formation in the kidney and lungs is a conspicuous feature of two of the three experiments. Two control experiments in which Bacillus pyocyaneus was injected into the jugular vein showed the absence of lymphatic thrombosis and the scant distribution of abscesses.

In two experiments Staphylococcus pyogenes aureus was injected into the circulating blood after ligation of the thoracic duct. In one instance thrombosis occurred; in the other there was no thrombosis and communication of the thoracic duct with the subclavian vein was reëstablished within ten days.

In one instance the thoracic duct was ligated, but no bacteria were injected into the circulation. The animal gave evidence of bronchitis and bronchopneumonia and the wound became infected with a microörganism resembling that of canine distemper. There were areas of suppuration near the thoracic duct and extensive thrombosis within it.

Thrombosis in lymphatics occurs under conditions which are dependent upon the peculiar constitution of lymph. Lymph contains no platelets and is deficient in thrombokinase. The penetration of thrombokinase into lymphatics may bring about thrombosis. This condition is fulfilled whenever cells in contact

with the lymph stream undergo necrosis. The larger lymphatics of the body have been studied because they offer a favorable opportunity for experiment. There can be little doubt that similar changes may occur in the small lymphatics distributed throughout the tissues.

One purpose of the experiments which have been described has been to determine the changes which occur when lymphatics of the part are so obliterated that reëstablishment of lymphatic circulation is temporarily or permanently prevented. This purpose has been only partially accomplished. Occlusion of the thoracic duct by ligature is followed by transient edema of the retroperitoneal tissues. Collateral lymphatic circulation is quickly established and new channels are found. The same process occurs when the thoracic duct undergoes partial thrombosis. In one instance a new channel, found by injection of India ink into an abdominal lymphatic, had been established within two days on the right side of the aorta and esophagus joining the right thoracic duct, and in another experiment a similar channel within the posterior mediastinum had reëstablished communication with the venous system at the site of junction between the ligated thoracic duct and the vein. Following occlusion of the duct groups of conspicuous dilated lymphatics are often found below the peritoneum over and immediately about the root of the mesentery. It is not improbable that repeated occlusion and thrombosis of newly formed channels would result in the formation of lymphatic varices similar to those not infrequently found in tropical countries in association with the lodgement of filaria in the lymphatic system.

The relationship between thrombosis of lymphatic channels and bacterial infection recalls the well-recognized occurrence of vascular thrombosis in association with bacterial infection. The bacteria which have been tested lodge apparently in the occluded lymphatic and doubtless produce injury of such character that the necessary factor, namely, thrombokinase, is liberated into the lymph. In one instance bacteria were found within the lumen of the thrombosed lymphatic duct, whereas in other experiments there was acute inflammation of the wall of the vessel. It is not improbable that free flow of lymph containing bactericidal sub-

stances is one of the most important factors in resisting bacterial infection.

The experiments with Bacillus pyocyaneus suggest that temporary or permanent occlusion of lymphatics by thrombosis may have an important influence upon the localization and development of pyogenic infection. In experiments which have been described a severe pyemia with abscesses in large number in kidneys and lungs occurred in association with occlusion and thrombosis of the thoracic duct, whereas abscess formation following the injection of the same culture into normal animals was inconspicuous. This suggestion is supported by the repeated occurrence of fever and local inflammation in association with elephantiasis presumably associated with lymphatic obstruction.

Conclusions. The slow coagulation of lymph is hastened by the addition of thrombokinase, and thrombosis within lymphatic channels occurs when thrombokinase is liberated by the tissues in the wall of the lymphatic. Necrosis of cells in contact with the lymph stream favors thrombosis within lymphatic vessels by bringing thrombokinase into contact with the circulating lymph.

After ligation of large lymphatic channels thrombosis may be caused by injection of bacteria (Bacillus pyocyaneus, Staphylococus pyogenes aureus) into the blood or by infection of the tissues in the neighborhood of the lymphatic channel.

Occlusion of the thoracic duct or of large lymphatic trunks is followed by transient edema, which is relieved in part at least by establishment of collateral lymphatic circulation.

After ligation of the thoracic duct, flow of lymph into the vascular system may be reëstablished within from two to four days (*a*) by formation of a new channel entering the proximal part of the ligated duct or (*b*) by collaterals freely joining the right thoracic duct; (*c*) in other instances no reëstablishment of communication with the vascular system could be demonstrated, but there was no widespread edema.

Copious chylous ascites may follow occlusion of the thoracic duct in association with injury to a mesenteric lymphatic vessel. In a few instances continued diarrhea follows occlusion of the thoracic duct.

ANTITYPHOID VACCINATION IN THE ARMY

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The year 1912 was eventful in the history of antityphoid vaccination in this country, as it enabled us, through the enforcement of compulsory vaccination, during the latter part of 1911, to collect, for the first time, statistics for the army and navy, covering a full calendar year.

The following table gives a complete statement relative to typhoid fever among enlisted men of the army, stationed in the United States proper, for the past eleven years:

Table I.—Typhoid Fever—United States. Enlisted American Troops.

Year.	Mean strength.	Absolute cases.	No. of deaths.	To each 1000 soldiers of the command, the ratios are. For cases.	For deaths.
1901	26,515	250	17	9.43	0.64
1902	39,736	341	34	8.58	0.86
1903	42,264	246	12	5.82	0.28
1904	43,940	247	12	5.62	0.27
1905	42,834	153	13	3.57	0.30
1906	40,621	230	12	5.66	0.28
1907	35,132	124	7	3.53	0.19
1908	46,316	136	11	2.94	0.23
1909	57,124	173	16	3.03	0.28
1910	55,680	129	9	2.32	0.16
1911	55,240	44	6	0.80	0.11
1912	58,119	15	2	0.26	0.03

In considering this, and the following charts and tables, it is necessary to know to what extent vaccination has been used. It was begun in March, 1909, and during that year, 830 volunteers from the army were immunized. Many others, not belonging to

the service, were treated, making the total number of doses given 5106 to 1987 persons.

In 1910, 16,093 persons were treated, most of whom belonged to the army.

Vaccination was voluntary during the first portion of 1911, but on the 9th of March, compulsory vaccination was ordered for the Southern Maneuver Division, about 20,000 men. The next step, June 9, 1911, was the extension of this order to all recruits, since which time 2000 to 3000 have received the prophylactic treatment each month, at the same time being vaccinated against smallpox.

The last and most important step was the extension of compulsory prophylaxis to all persons in the service under forty-five years of age; this was ordered on September 30, 1911.

In the United States proper, the order was not fully executed until the first of January, 1912. In the Philippines it was not carried out until the first quarter of 1913.

By noting the mean (average) strength of the army in these years, it will be seen that until well along in 1911 the proportion of vaccinated to unvaccinated was quite small, and that not until 1911 and 1912 was the number large enough to exert a decided influence upon typhoid morbidity and mortality.

Table II differs from Table I in that it includes officers with the enlisted men, and also shows the number who developed the fever before immunization could be carried out—cases undoubtedly infected before enlistment. The number of cases and deaths among the vaccinated for each year is also given.

TABLE II.—Typhoid, Cases, Deaths, etc., Officers and Men, U. S. Proper.

Year.	Total cases.	Total deaths.	Infected prior to enlistment.	Among the vaccinated. Number of cases.	Number of deaths.
1909	170	16	?	1	0
1910	139	10	?	4	0
1911	44	6	?	7	0
1912	18	3	5	6	0

Table III is for the entire army, American and native, officers and enlisted men, at home and abroad, and covers a period of eleven years.

TABLE III.—Typhoid Fever, 1901–1912, for the Whole Army at Home and Abroad, Officers and Enlisted Men.

Year.	Mean strength.	Cases. Number of.	Cases. Ratios per 1000 of mean strength.	Deaths. Number of.	Deaths. Ratios per 1000 of mean strength.	Percentage of total cases.	Occurring among those who were vaccinated. Cases.	Occurring among those who were vaccinated. Deaths.
1901	81,885	552	6.74	74	0.88	13.0		
1902	80,778	565	6.99	69	0.85	12.2		
1903	67,643	348	5.14	30	0.44	8.6		
1904	67,311	293	4.35	23	0.33	7.8		
1905	65,688	206	3.14	20	0.30	9.7		
1906	65,159	373	5.72	18	0.27	4.8		
1907	62,523	237	3.79	19	0.30	8.0		
1908	74,692	239	3.20	24	0.31	10.0		
1909	84,077	282	3.35	22	0.26	7.8	1	0
1910	81,434	198	2.43	14	0.17	7.1	7	0
1911	82,802	70	0.85	8	0.10	11.4	11	1
1912	88,478	27	0.31	4	0.044	14.8	8	0

TABLE IV.—Typhoid Fever, 1911, Officers and Enlisted Men, United States Army.

	Cases.	Ratio per 1000 of mean strength.	Deaths.	Ratio per 1000 of mean strength.	Cases in immunized persons.	Deaths in immunized persons.
United States	44	0.76	6	0.10	7	0
Philippine Islands:						
American troops[1]	12	0.88	0	0	3	0
Transports	1	0.56	1	0.55	0	0
Native troops[2]	12	2.28	0	0	0	0
Porto Rico:						
Native troops	1	1.78	1	1.78	1	1
Total army	70	0.91	8	0.10	11	1
Paratyphoid fever:						
United States	1	0.02	0	0	0	0
Panama	1	4.69	0	0	0	0

TABLE V.—Typhoid Fever, 1912, Officers and Enlisted Men, United States Army.

	Mean strength.	Cases. No.	Cases. Ratio.	Deaths. No.	Deaths. Ratio.	Cases in immunized persons.	Deaths in immunized persons.
United States	61,405	18	0.29	3	0.0475	6	0
Alaska	1,251	0	0	0	0	0	0
Philipines:							
American Troops and Officers	13,115	5	0.38	0	0	0	0
Native troops	5,407	3	0.55	1	0.1820	1	0
China	1,141	0	0	0	0	0	0
Hawaii	3,549	1	0.28	0	0	1	0
Panama	807	0	0	0	0	0	0
Porto Rico	629	0	0	0	0	0	0
Transports	1,174	0	0	0	0	0	0
Total	88,478	27	0.31	4	0.044	8	0

[1] Including officers.

[2] No prophylactic used.

The distribution of typhoid among various groups is shown in Tables IV and V.

In all tables, morbidity rates are based upon the strength of the army reported to the Surgeon-General by medical officers. As not all troops receive medical attention from members of the Medical Corps, the records of the Adjutant-General are used in computing death-rates, as all deaths, however occurring, are reported to that office.

Charts I and II correspond to Table I.

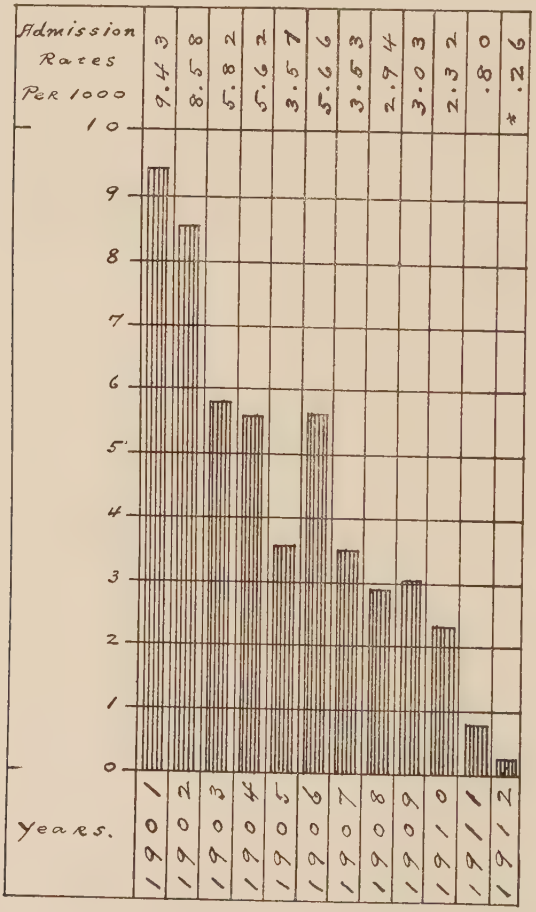


CHART I.—Admission rates for typhoid fever. United States (enlisted men).

Chart III shows the constantly non-effective ratio, due to typhoid and paratyphoid fever, for the past ten years. This ratio is the true measure of loss of efficiency in the army from typhoid

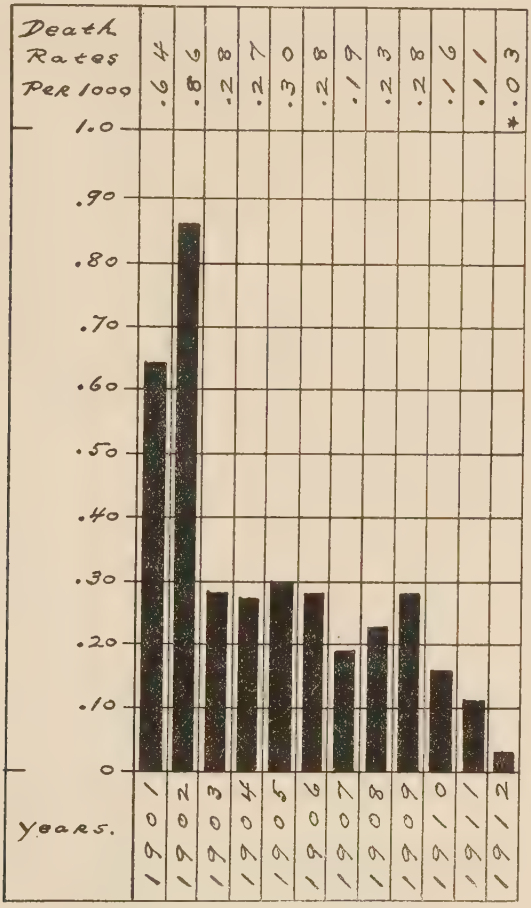


Chart II.—Death-rates for typhoid fever. United States (enlisted men).

fever, showing, as it does, the number of days lost per thousand of mean strength for the year, including both days sick in hospital and during period of convalescence.

This chart shows, as do the others, the remarkable improvement

due to vaccination. The year 1908 represents the best ever accomplished by pure sanitation alone. The striking improvement in 1911 and 1912 is due entirely to vaccination.

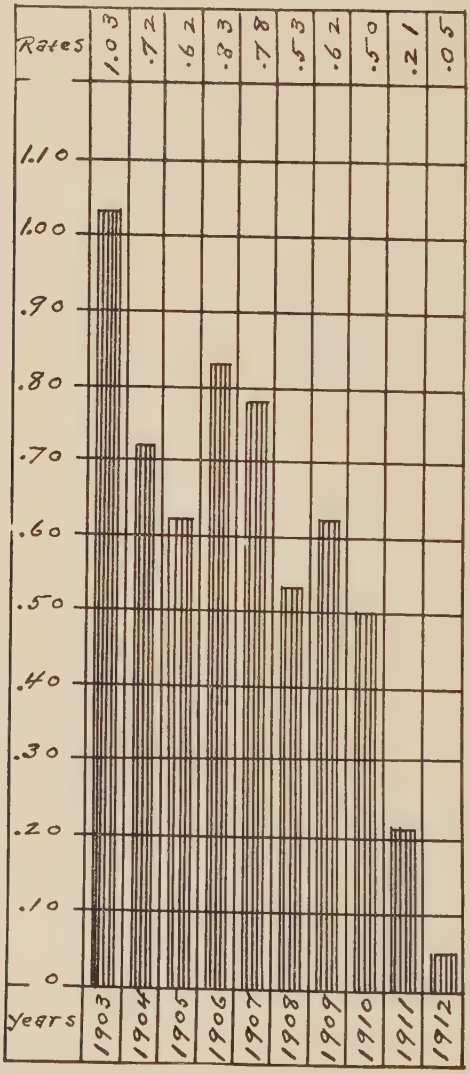


CHART III.—Non-effective rates for typhoid fever for the army, officers, American troops, Porto Ricans, and Philippine scouts. Includes paratyphoid fever.

During the first half of 1913 no cases have been reported; the last case occurred on December 9, 1912. The patient was an officer who had not been vaccinated, because of a history of previous typhoid fever.

The significance of a statistical table is not readily apparent, without compariosn with familiar facts. For this reason Table VI, comparing typhoid death-rates in the army with those in civil life, has been prepared.

TABLE VI.—Death-rates per 100,000 Population.

Year.	Army. U. S. Proper.	Civil Life, U. S. Census.
1903	28	34.1
1904	27	31.7
1905	30	27.8
1906	28	31.3
1907	19	29.5
1908	23	24.3
1909	28	21.1
1910	16	23.5
1911	11	21.0
1912	3	?

From this table it is apparent that even before the introduction of vaccination, there was less typhoid fever in the army, as a rule, than among the civil population of the registration area, and that since 1910 the army death rate has fallen far below that found in civil life.

The thought readily suggests itself, therefore, that extensive use of antityphoid vaccine in civil life would bring about corresponding improvement. An examination of Chart III, showing the diminution in the number of sick days per annum, should be sufficient to convince any contractor, or other large employer of labor, or the head of any department, school, or institution of the gain in efficiency which can be brought about by vaccination.

The duration of protection remains unknown. The old idea, that the immunity lasted only so long as agglutinins or other antibodies were present in the blood, has been discredited; experience shows them present as long after vaccination as after typhoid fever itself, and this gives, as we know, protection for life.

The immunity, no doubt, diminishes gradually, as after vac-

cination against smallpox. Since, in our service, all persons under forty-five are vaccinated, there is no group of unprotected persons with which to compare the immunized. It is the practice at present to revaccinate at the beginning of each four-year period of enlistment, against both smallpox and typhoid fever, not because all immunity has disappeared, but for the reason that it seems unwise to trust to anything less than the maximum immunity obtainable.

The vaccine is prepared from a single, selected strain of the Bacillus typhosus, grown for eighteen hours on agar, and suspended in normal salt solution. The bacilli are killed by heating to 54° C. for one hour, and 1 per cent. of tricresol is added to protect against subsequent contamination.

The first dose contains 500,000,000 bacilli, the second and third 1,000,000,000 each; the usual interval is ten days between doses, although in many instances the three doses are given on three successsive Saturday afternoons, since a weekly interval is often more convenient.

The army is as well protected against smallpox as repeated vaccination can make it, yet during the past four years vaccination has failed to protect against smallpox in sixty-five instances, two of which were fatal. During the same period, although among a smaller number of men, antityphoid vaccination has failed only twenty-seven times, and there has been only one death (from hemorrhage) among the immunized.

TABLE VII.—Comparison of Smallpox and Typhoid Vaccination, Entire Army, and Enlisted Men.

	Smallpox.			Typhoid.		
Year.	Number vaccinated.	Cases.	Deaths.	Number vaccinated.	Cases.	Deaths.
1909	74,692	7	0	830	1	0
1910	81,434	17	1	16,093	7	0
1911	82,802	20	0	30,000?	11	1
1912	88,478	9	0	88,478	8	0
		53	1		27	1

During the past four years there have been immunized, approximately, 200,000 persons, entirely without fatalities or any outward results. In the army none but the healthy are immunized, any

illness, of whatever nature, automatically postpones vaccination until recovery.

The prophylactic consists, as has been stated, of a suspension of dead typhoid bacilli in salt solution. Metchnikoff and Besredka, Castellani and others have proposed the use of vaccines prepared from living, avirulent bacilli. Had we been less successful with the present prophylactic, a living vaccine might have been considered: as it is, however, there are certain insurmountable objections to it. Compulsory vaccination could not be enforced and there may be some danger in handling a living vaccine, even though it be harmless when injected subcutaneously; it might still cause infection through the intestinal tract.

The practice of vaccinating against typhoid has been a pronounced success in the naval and military services, in hospitals, schools, institutions, pleasure seekers' and contractors' camps, especially those located on water-sheds, in fact, everywhere in civil and military life where it has been used. We feel that its more general use, especially among the young, is advisable. The fact that it occasionally fails to confer complete protection, is not a valid objection to its use, but rather an indication for its repetition, at intervals to be determined upon in the future. It will certainly be as efficacious in civil life as in the army, and its more general use will hasten the time when typhoid fever will become a negligible factor in our public health problems.

DISCUSSION

Dr. A. C. Abbott: There can be no division of opinion as to the propriety of the position taken by the army in this matter; the figures presented by Major Russell are convincing to the last degree.

The method employed by the army could be used equally well by any municipality. But what of the personal inconvenience to inoculated persons? Soldiers are usually in the pink of condition; and, moreover, it requires an illness of rather sharp severity to be taken account of by them. The general populace are apt to take a different view of antityphoid vaccination and its occasional reactions. Is there any modification possible to

make this method available for general use? My reason for asking this is that Gay, of California, has devised a way to lessen the reactions following serum inoculation, and it occurred to me that it might be applied to vaccine therapy.

Dr. W. H. Park: Impressed by the results in the army, we have in New York undertaken to immunize the members of families in which a case of typhoid fever has occurred. But we have not reached the point of forcing it upon those who raise objections.

Dr. W. S. Thayer: What impression has been gained as to the duration of the protection afforded by antityphoid vaccination? And what is Major Russell's feeling as to the supposed negative phase of Wright?

I think I may safely take the liberty of expressing the sense of pride we all feel in the monumental work achieved by Major Russell and his co-workers in the army.

Dr. George M. Kober: I wish to endorse the plea for a more general application of antityphoid vaccination in civil life. If the figures presented here by Major Russell are not conclusive, then reason and logic are mere accomplishments. The Army is composed, by reason of the average age of the enlisted men, of very susceptible individuals; we should therefore expect a high morbidity rate, but we find that universal compulsory vaccination has greatly reduced the rate below the average for civil life.

We do not and cannot know the duration of the immunity conferred, but we do know that it protects for the present and we may at least hope it will be found to protect for life. I think we are backward in pressing this prophylactic measure into civil life. I myself have been inoculated, and I can testify from experience that the resulting slight reaction is not sufficient to cause great inconvenience or to be a valid objection to the vaccination.

Dr. V. C. Vaughan: Since Jenner made his first experiments with vaccinia, no better mode of protection against smallpox has been devised than inoculation with the virus of cowpox; and I think that in view of the magnificent results obtained by Major Russell with his original vaccine, he is quite right to stick to that vaccine.

Notwithstanding the undoubted immunity which can be conferred on the populace by vaccination, we should still stop to see what is the minimum death rate for the typhoid that may be obtained without vaccination, but with the very best hygiene.

At the University of Michigan there are assembled about 5600 young men and women from all over the State. Since 1884 we have taken special precautions against typhoid fever in that community. The water-supply is examined weekly or if necessary, daily; if the colon bacillus is found, notices are sent out requiring the people to boil the water. Strict supervision is maintained over the milk supply. The death rate for typhoid in Ann Arbor for many years has been less than 15 per 100,000; which indicates what may be done by mere sanitation. The frequent migrations of the students brings some typhoid into the community from other parts of the State, and better results could be obtained with a stationary population, as has been done in Munich.

I believe that vaccination has been most useful in the army, and I have not the slightest adverse criticism to make of the admirable work of Major Russell; but in a critical study of the statistics I would call attention to two facts: there are no military camps now at all comparable with the camps during the Spanish War; and the year 1912 was not a typhoid year.

Dr. M. H. Fussell: I should like to ask Major Russell if he regards the commercial vaccines for antityphoid inoculations as perfectly reliable?

Dr. A. C. Abbott: It seems to me that the Army Medical Corps has demonstrated absolutely that vaccination will stop typhoid fever; and there ought to be no hesitation or delay about applying this prophylactic measure in civil life, especially if some modification of the vaccine can be devised to lessen the reaction.

Dr. George Dock: I think it would be unfortunate to have an exaggerated idea go abroad as to the severity of the reactions. Surely enough vaccinations have been done under critical observation to demonstrate that there are no ill effects.

Dr. Thomas McCrae: I wish to ask Major Russell three questions:

1. What rules have been laid down governing revaccination?
2. Are there any figures as to the frequency of severe reactions after revaccination?
3. Do you vaccinate the soldiers who have had typhoid fever.

Major Russell: In answer to the various questions I would say: We have had no evidence of the existence of a negative phase; we have no hesitation in vaccinating contacts. The length of the period of immunity produced is not known. The English experience has been that after two and one-half years the immunity of vaccinated troops is no better than others. Our practice is to vaccinate with each enlistment.

Our statistics on the severity of reactions are based entirely on the temperature records; the subjective symptoms are not taken into account. Soldiers do not react differently from civilians; in fact, soldiers were civilians a few months before.

Severe reactions may be followed by loss of weight (which is quickly regained) and by nausea, vomiting, and diarrhea. I have not seen a case of albuminuria due to vaccination, but I believe it may occur.

I hope some day to see a vaccine which will not produce a general reaction; but we do not know how to make it yet. As a general rule, systemic reactions are absent in children and young people.

The problem in the army is very different from that to be met in civil life; military necessity requires us to ignore the few severe reactions. In camps there may always be bacillus carriers and so vaccination must be done for all. What may be done in civil life by sanitation is not a factor in military life, because soldiers may at any time be required to go and to live where there is no sanitation at all.

The Ann Arbor typhoid death rate was given by Dr. Vaughan as 15 per 100,000; but the army rate was 3 per 100,000, so that something can be done to improve the Ann Arbor rate.

I know of no reason why commercial vaccines should not be reliable.

Reactions following revaccination do not differ from those following the primary vaccination.

If there is a record on the army books of a soldier's having had typhoid fever, he is not vaccinated.

STUDIES IN DIABETIC ACIDOSIS

By A. I. RINGER, M.D.
PHILADELPHIA

(BY INVITATION)

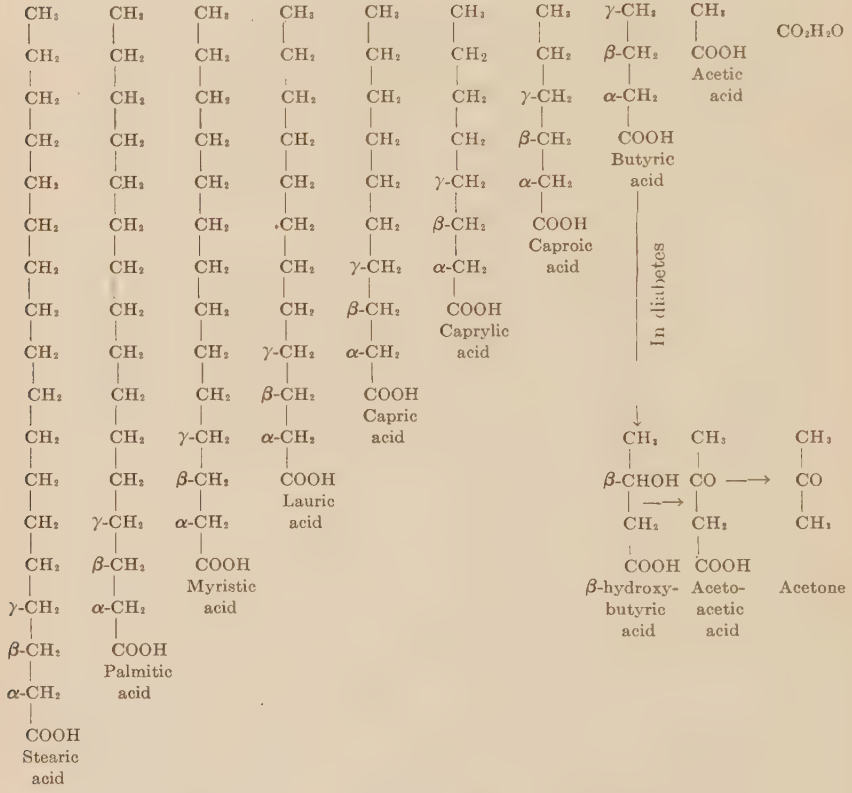
(From the Department of Physiological Chemistry of the University of Pennsylvania, Philadelphia, Pa.)

Acidosis is a condition characterized by the appearance of what are known as acetone bodies in the blood and subsequently in the urine of an individual. These acetone bodies are beta-hydroxybutyric acid, aceto-acetic acid, and acetone. To trace the development of our knowledge of these bodies and their role in the pathology of disease and diabetes, would mean to write a history of the development of physiological and pathological chemistry, since no group of compounds occupies so singularly central a position in the intermediary metabolism of protein and fats, and are so closely related to carbohydrate metabolism.[2] Our conception of the origin of these bodies, their place in the intermediary metabolism, and their fate in the body in health and disease has varied with our theories of the metabolism of protein, carbohydrates, and fats, and it was not until it was learned that the fate of the protein molecule in the animal body is equivalent to the fate of its individual amino-acids, and that the fate of the fat molecule is equivalent to the fate of glycerol and the fatty acids, that the genetic phase of the acetone bodies was made clear.

It is now well established that the acetone bodies find their origin mainly in the catabolized fats.* In health, the only end-products of fat metabolism are CO_2 and H_2O. The fatty acids of the body consist of palmitic, stearic, and oleic acids, all of which contain an even number of carbons in their respective molecules

* The proteins can contribute to the formation of acetone bodies insofar as they contain leucin and tyrosin.

(16, 18, and 18). In the animal body palmitic and stearic acids are known to undergo successive oxidations in the beta-position,* each time giving rise to a fatty acid with two carbons less as intermediary bodies. Thus:



The complete catabolism of the fatty acids as pictured above is not an entirely independent process, but is largely dependent upon the presence of carbohydrates in the diet, and upon the individual's ability to utilize carbohydrates. In prolonged starvation and in diabetes, conditions in which the catabolism of carbohydrates is very much restricted, the butyric acid molecule, which is always formed in the intermediary metabolism of the

* The carbons in the fatty acid molecule are designated by the letters of the Greek alphabet, in relation to the position they occupy with regard to the terminal carboxyl radical.

fatty acids, becomes only incompletely oxidized, *i. e.*, only to beta-hydroxybutyric acid and aceto-acetic acid, which, to a certain extent, give rise to acetone. These bodies are burnt with great difficulty and are eliminated in the urine. The amount that appears in the urine is directly proportional to the degree of disturbance in the carbohydrate utilization.

Since these facts became known, it became of great interest to find the nature of the influence of the carbohydrate molecule on the metabolism of fatty acids and on the prevention of the ketone formation.* The questions that have arisen are:

1. Do these acetone bodies represent a reaction *de novo* that has set in, in the metabolism of the diabetic or starving individual, and are they the products of a pathological catabolic process on the part of the fatty acids, or are they bodies which play a role in normal intermediary metabolism, but which can no longer be catabolized by the body?

2. What is the mechanism of antiketogenesis? In what way and by what process does the carbohydrate (glucose) molecule prevent the formation of the acetone bodies or cause their combustion? Is this property of the glucose molecule inherent in the entire molecule, in its peculiar chemical structure, or is it dependent upon the fact that the glucose molecule contains certain radicals which favor this antiketogenetic reaction? Does the glucose molecule itself exert this influence, or do the products of its metabolism possess this property?

The early students of diabetes realized the importance of these problems. Naunyn[3] suggested that the glucose may cause "secondary oxidation" of the acetone bodies. Rosenfeld said that "the fats burn only in the fire of the carbohydrates," which expression was modified by Magnus-Levy[5] by inserting the word "completely" after the word "burn."

All these conceptions *characterize* the condition, but in no way *explain* it. In this series of experiments our object was to find out the *modus operandi* of the antiketogenetic action of glucose.

* Because aceto-acetic acid and acetone contain the =CO radical they are known as ketones. The mother substances are known as ketogenetic, and substances which prevent their formation are known as antiketogenetic.

The experiments were performed on female dogs which were made diabetic by the daily subcutaneous injection of one gram of phlorhizin ground up in olive oil. Such dogs, under fasting conditions, may eliminate 100 to 500 mg. of acetone and aceto-acetic acid, and 0.5 to 4.0 grams of beta-hydroxybutyric acid per twelve hours. The dogs were kept in metabolism cages suitable for the collection of voided urine. At the end of each period of twelve hours the dogs were catheterized and the bladder washed with warm distilled water. The urine was usually analyzed for its optical activity, nitrogen, glucose, ammonia, acetone, aceto-acetic acid, and beta-hydroxybutyric acid. The nitrogen was determined by Kjeldahl's method, glucose by Allihn's, ammonia by Folin's, acetone, aceto-acetic acid, and beta-hydroxybutyric acid by Schaffer's method.

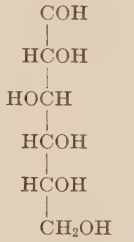
The principal line of reasoning followed in these experiments was this: the glucose molecule must exercise its antiketogenetic powers in one of three ways:

1. It acts because of its peculiar chemical structure, and the entire molecule is necessary for the reaction, in which case a change of either part should be followed by the loss of its antiketogenetic powers.

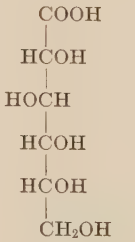
2. It acts because it possesses certain radicals, either an aldehyde or secondary alcohol, etc., in which case other compounds possessing these radicals should also possess antiketogenetic powers.

3. It acts because of products that are formed in its intermediary metabolism, and these products possess antiketogenetic powers.

The substance most similar to the glucose molecule is *d*-gluconic acid.



Glucose



Gluconic acid

In a series of experiments 20 and 25 grams of the calcium salt of gluconic acid were given *per os* to two dogs. In neither case was there a diminution in the elimination of acetone or beta-hydroxybutyric acid. That gluconic acid burns in the body has been proved beyond doubt by the works of Baumgarten.[6]

When one considers the close similarity that obtains between the structure of the gluconic acid molecule and that of glucose, and notes that the only difference between them is in the presence of the aldehyde radical in glucose, which in gluconic acid is oxidized to a carboxyl, one feels justified in drawing the tentative conclusion that *upon the aldehyde radical of the glucose molecule rests its pharmacological action.*

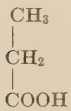
This theory gains greater weight when we realize in what a complexity of unions the glucose molecule enters because of the combining powers of the aldehyde radical. There are a great many compounds, especially alcohols and ketones, which, when administered into the animal body, enter into chemical union with the aldehyde radical of the glucose molecule, giving rise to glucoronates. O. Newbauer[7] made a very systematic study of all the alcohols that give rise to glucoronates. He found that the secondary alcohols possess great powers of effecting this union with the aldehyde radical of the glucose molecule.

What is the object of this union? Has this widespread, almost universal reaction any significance? Pharmacologists teach us that the union is brought about for detoxicating purposes, but this teaching is not at all binding. It may be true in the case of the aromatic compounds, which are eliminated in very large quantities, but not in the case of the aliphatic alcohols and ketones, for the amount excreted is very small in comparison with the amount burnt.

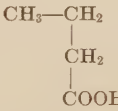
We feel convinced that the general reaction, *i. e.*, the union between the alcohols and ketones with the aldehyde radical of the glucose molecule has as its object the combustion of that substance.

From the relationship existing between butyric and isobutyric acids, it is evident to what an extent the configuration of the molecule influences its physiological fate. Normal butyric acid

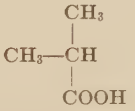
may be considered propionic acid in which an hydrogen atom in the beta-carbon is replaced by a methyl radical, whereas isobutyric acid has an hydrogen atom in the alpha-carbon replaced by a methyl radical.



Propionic acid

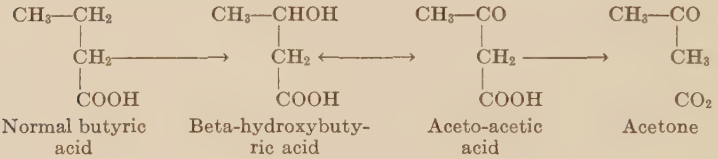


Normal butyric acid or beta-methyl propionic acid

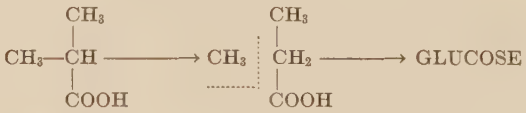


Isobutyric acid or alpha-methyl propionic acid.

This difference in the structural configuration of the molecule determines the difference in the course of the substance in intermediary metabolism. Normal butyric acid gives rise to beta-hydroxybutyric acid, aceto-acetic acid and acetone; whereas isobutyric acid gives rise to glucose.[8]



Normal butyric acid — Beta-hydroxybutyric acid — Aceto-acetic acid — Acetone



Isobutyric acid — Propionic acid

We are inclined to believe that one of the functions of the glucose molecule in normal metabolism is to make beta-hydroxybutyric acid, which must arise constantly in the catabolism of the higher fatty acids, combustible. The glucose molecule accomplishes this by combining its aldehyde radical with the secondary alcohol, thus converting the derivatives of normal butyric acid into iso-compounds, and by changing their configuration, rendering them oxidizable.

Working along this line, we are studying the effects of different

substances, which either themselves or the products of their metabolism possess distinct antiketogenetic properties.

In conclusion, we may state that it is very surprising to find with what regularity and consistency the diabetic organism responds to certain definite chemical compounds in one way or another. We are beginning to realize, more and more, that the problems of diabetes are problems of pure chemistry; that to get at the laws which govern the metabolism of the diabetic, it is necessary to dissect the chemical substances that play a part in the intermediary metabolism of the diabetic patient or animal, and study the effect of each substance individually, and thus we may hope to get at the true seat of the disturbance.

Since the presentation of this paper, additional evidence has been accumulated which strongly supports this theory. The full report of all the experiments will appear in the *Journal of Biological Chemistry*.

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8. Ringer, Frankel and Jonas. Loc. cit.

DISCUSSION

Dr. Theodore C. Janeway: I think I am voicing the feeling of all our members in saying a word of appreciation of the exceeding great value of this fundamental work presented by Dr. Ringer. The facts here presented by him seem to point definitely and most hopefully to the solution of a great and hitherto exceedingly dark problem.

We are so taken up with the fascinating problems of bacterial therapy, that we are apt to forget that pure chemistry is going forward to similar practical ends in its own way and is doing much to show us how to combat diseases due to pure chemical poisons.

I think that Dr. Ringer's work comes nearer than any in the world to showing exactly how to combat acidosis. Only one more step needs to be taken to find some practical way to utilize for food in diabetes only those fats whose molecules contain the uneven number of carbon atoms; and I confidently look to see that step taken.

Dr. J. B. Leathes: Dr. Ringer has courageously attacked a huge subject. The really important feature of the paper, from a practical standpoint, may have escaped attention. The dietetic problem in diabetes is to supply safely enough food to sustain the necessary body energy, and as the three carbon fatty acids do not break down into the poisonous beta-oxybutyric acid, but into harmless glucose, we may be able to find some food by which we may utilize this knowledge.

Dr. Ringer: I would like to add to Dr. Leathes' remarks that diabetics may produce fairly large amounts of acetone bodies without presenting any symptoms. Very small amounts of these substances arise from leucin, tyrosin, etc., and I have seen patients sustain large amounts with fair comfort. So that two or three grams of acetone bodies from protein combustion may well be withstood if that from the fatty acids can be eliminated. Thus the problem is still further simplified.

PNEUMONIC HEMIPLEGIAS

By CHARLES F. WITHINGTON, M.D.
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Cerebral accidents in pneumonia are not very rare. They may be divided into two classes:

I. Those caused by gross anatomical lesions, such as meningitis of pneumococcal origin, thrombosis, embolism, softening, abscess, etc.

In a recent paper[1] I have shown that among 7600 pneumonic patients there were found 21 cases of pneumococcus meningitis, 4 of embolism, 2 of thrombosis, 1 of softening, 3 of abscess, 2 of edema, 2 of "hemiplegia," 1 of transient aphasia.

II. There remains a second group of hemiplegias to which exclusive attention will be given in this paper. They occur generally in young and rather vigorous people, and their prognosis is relatively much better than that of the first group. As many recover, there is in such cases a lack of postmortem evidence to show what lesion, if any, existed.

Four principal explanations of the hemiplegias of this group have been offered.

1. Encephalitis, of the Strümpel type.[2] Hoppe-Seiler gives pneumonia as one of the rarer causes of encephalitis. The relation of the latter condition to influenza is now generally recognized and it is possible that it is to pneumonias of influenzal origin that encephalitis has a particular relation. Comby[3] has shown that encephalitis is related to other infections, like pertussis, enteritis, mumps, typhoid fever, etc. He says that most of these cases of

[1] Medical and Surgical Reports of the Boston City Hospital, 1913.
[2] Lehrbuch der Greisenkrankheiten, von Schwalbe, 1909, p. 236.
[3] Soc. Médicale des Hôpitaux de Paris, xxviii, 570 et seq.; also Le Bulletin Médical, 1906, No. 5.

toxic encephalitis recover and give no chance for being studied by autopsy but cites a few autopsies where there "were red discolorations of the cortex, points of hyperemic swelling from congestion and serum, the little vessels engorged with blood, sometimes thrombosed, around them numerous extravasated leukocytes, sometimes the vascular tissues thickened and infiltrated with polynuclear leukocytes; miliary hemorrhages, the neuroglia altered in the whole inflammatory zone; serofibrinous infiltration of the stroma and swelling of the cells, chromatolysis of nerve cells, disappearance of their prolongations, dissociation of nerve fibers, granular bodies, etc." Such cases show clinically a sudden onset in health or the midst of an infectious disease, convulsions, coma, a "meningitique state," limited paralysis with aphasia or mutism. The hemiplegia is usually spasmodic, with exaggerated reflexes. These may be associated with choreic or athetotic movements, tremors like those of disseminated sclerosis, etc. Comby will not admit the diagnosis of meningitis sometimes offered in such cases unless it is confirmed by lumbar puncture.

Leichtenstern[1] describes cases of primary acute hemorrhagic encephalitis as occurring in various infectious, diseases including ulcerative endocarditis and influenza.

Mollard and Dufourt[2] in a case of a man taken on the seventh day of pneumonia with marked cerebral symptoms but giving by lumbar puncture a clear fluid and dying the next day, demonstrated an encephalitis. They quote a thesis of Chappet in which the writer was able to show only one case of encephalitis due to pneumonia confirmed by autopsy, but cited several pneumonic hemiplegias followed by recovery, where he believes a large part was played by encephalitis.

Some writers believe this encephalitis may come from a larval meningitis.

Strümpell in the last edition of his *Practice of Medicine* says: "It is of practical importance that according to more recent observations (the author, Oppenheim, and others) a *curable* form of encephalitis also occurs in adults."

[1] Deutsche medizinische Wochenschrift, 1892, p. 29.
[2] Lyon Médical, cxvi, 821.

Southard[1] says: "The diagnosis between hemorrhagic encephalitis and cerebral hemorrhage would be impossible on theoretical grounds." He attempts the differentiation between encephalitis and hemorrhage by saying: "Practically the paralyses which characterize hemorrhagic encephalitis do not occur simultaneously with the onset of drowsiness or coma. The signs of some cerebral disease are obvious long before paralyses or convulsions have set in. The paralyses of hemorrhagic encephalitis may increase in intensity from time to time in the course of several hours or a day, presumably owing to the gradual development of inflammatory lesions with oozing of blood."

In the cases of pyogenic encephalitis he finds that the organism concerned is more often the staphylococcus pyogenes than pneumococcus, in the ratio of 6 to 2.

2. A second assigned cause of pneumonic hemiplegia is hysteria. This is particularly emphasized in a thesis by Boulloche, of Paris (1892). Daireaux[2] is inclined to favor the view at least in some cases.

3. Circulating organisms. If pneumonia is, as is now believed, a septicemia, there is little doubt that its organism may be carried in the blood stream to the brain. And as a matter of fact, many organisms have been found there. Mollard[3] says that Pfühl has found in the brain the bacillus of Pfeiffer, Kirschman that of Eberth, and Leichtenstern the meningococcus.

Fränkel has investigated the distribution of various organisms in the brain. As to pneumococcus he finds two groups: (*a*) Pure pneumococcus infection; (*b*) associated pneumococcus infection. But of five cases where pneumococcus was abundant in the blood, in two the brain was sterile and in the case of all the organisms the brain was found purer than the blood.

Southard termed certain cases bacterial apoplexy. They all occurred in young people between twelve and twenty-two.

It is a little difficult to understand how circulating organisms should so far mass themselves in the brain as to produce hemiplegia.

[1] Osler's Modern Medicine, vol. vii.
[2] Archives générales de Médecine, 1906, p. 2241.
[3] Loc. cit.

4. Circulating toxins. The same objection last mentioned applies to regarding circulating toxins as capable of producing focal lesions by direct action.

The role of toxins is more probably an indirect one.

Stephan in 1889 attributed the symptom to a vasomotor ischemia caused by ptomains in the blood which set up a vascular reflex analogous to what may occur in uremia. There is no anatomic change but the toxic substances when generated in one lung are apt to cause a reflex ischemia in the motor cells of the opposite side. Yet there has been much dispute on which side the paralysis is more likely to occur. Landrieux[1] says it is on the opposite side from the pneumonia. Daireaux[2] says it is oftenest on the right side.

Aufrecht,[3] after describing two cases of pneumonic hemiplegia in children, both of which recovered, suggests that the toxins cause a partial edema of the cerebral substance as a result of the changed constitution of the blood as may occur in uremia.

In his cases the pneumonia was of the upper lobes. He believes that in these cases the negative inspiratory pressure in the mediastinum is most reduced, thereby hindering the reflux of the blood from the cerebrum to the heart and so favoring the escape of serum from the arterial vessels and capillaries into the cerebral substance. But as he believes apex pneumonias are especially rare in children, so he finds such hemiplegias especially rare at that age

Given conditions producing cerebral edema, it seems reasonable, as has been suggested by Dr. Robert T. Edes, that hemiplegia might be caused if the posture of the patient made an excess of the fluid gravitate to one side of the brain It is a matter of common observation how readily an edematous effusion can shift its location, as from the legs to the back. I have found in our hospital but one case of marked cerebral edema occurring in pneumonia. This was in the service of Dr. F. H. Williams. A boy, aged eleven months, was said to have had two months previously convulsions and bronchitis. The day of admittance he had eleven convulsions, which are not stated to have been more on one side

[1] Revue géneral de Clinique et de Therapeutique, 1903, xvii, 129.
[2] Loc. cit., 1906, ii, 2241.
[3] Archiv für Kinderheilkunde, Band xi.

of the body than the other. Eight days later he died suddenly. There was found postmortem the last stages of gray hepatization of the left lower lobe. Edema of brain. Beneath the pia a well-marked collection of fluid, pia being raised above brain three-eighths of an inch, more marked on the left side. Brain otherwise normal. No tuberculosis.

Of the above mentioned theories of the production of pneumonic hemiplegia, it is probable that more than one is correct. We may follow the conclusions of Lesieur and Froment.[1] "The group of pneumonic hemiplegias embraces facts provisionally related to each other but for which a single pathogeny cannot be shown. Among sources which have been assigned, some (theories of congestion and cerebral edema) are founded on trivial lesions whose significance cannot be precisely defined in the absence of histological, chemical, and bacteriological examination. Others (theories of reflex and of hysteria) are rational, but are not as yet well enough demonstrated.

"One must then in various cases attribute pneumonic hemiplegias to ischemia by reason of insufficient cerebral circulation to meningitis, to meningoencephalitis, or to encephalitis.

"It is impossible at present to show with certainty which of these forms of pathogenesis is most frequent."

The phenomenon of pneumonic hemiplegia without gross lesion is not a common one. It appears usually about the second or third day from the onset of the pneumonia. In one case of Aufrecht it preceded the pneumonia by three days. Before the aphasia or paralysis there may be headache, syncope, bewilderment, or vertigo. There may be paresthesia of the side, followed by a frank hemiplegia. The aphasia may come suddenly without impairment of consciousness. "The type of the aphasia is usually ataxic as in lesions of the third left frontal convolution. The patient can pronounce only a few monosyllables more or less appropriate to what he wishes to say. At first the intellect is blunted and he cannot understand what is said to him, but after a few hours he indicates by gesture that he wishes to talk. There is always a

[1] Revue de Médecine, October, 1911 (special number in honor of the festival of Lépine).

paralysis of the right lower facial, the mouth is drawn to the left, tongue deviates to the right. The orbicular is intact. The hemiplegia may be complete, but oftener is limited to the face, tongue, and right upper extremity. The tendon reflex is only slightly affected. To the motor paralysis is often added a *vasomotor* with redness of the paralyzed area and then a demonstrable increase of temperature."[1]

Again, Lesieur and Froment[2] say: "There is no doubt that a certain number of pneumonic hemiplegias are due to an acute pneumococcic encephalitis. It is equally certain that this must not be considered as the only pathogenesis, to the exclusion of any other."

A good illustration of a typical transient pneumonic aphasia in a young subject is one by Doernberger,[3] which I will briefly condense.

A boy, aged three and a half years, was taken May 9 with coryza, followed by bronchitis. Six days later there was lobular consolidation throughout the right lower lobe, on the tenth day the same in right upper. On the sixteenth, consolidation of left upper and right middle lobes. Temperature, 104.3°. Same day loss of consciousness and of speech; pupils dilated, fixed; occasional scream; otherwise, stupid. No response to call. Slight stiffness of neck. No vomiting. Breathing regular, quick, uninterrupted. Patellar reflexes lost; slight stiffness of neck.

Seventeenth day, clonic spasms of left extremities; face drawn to left. These symptoms lessened and in three days the convulsions and meningeal symptoms had disappeared. On the twenty-sixth day the patient was afebrile; takes notice of playthings; makes contortions of face in vain attempt to spe .k; points at what he wants and frets until he gets it. On the twenty-seventh day of the disease and the eleventh of the aphasia, he speaks for the first time, yes and no. The speech then returns, at first slow and syllabic, but finally, with complete restoration.

In this case no lumbar puncture was made to exclude meningitis, but the brevity of the meningeal symptoms and the long con-

[1] Chantemesse, Soc. Médicale des Hôpitaux de Paris, 1893, x, 875.
[2] Loc. cit.
[3] Münchener méd. Wochensch., 1904, li, 833.

tinuance of the aphasia indicate that meningitis did not play the chief role.

The mortality of many of these toxic forms of pneumonia with hemiplegia does not seem to be greatly increased by the supervention of the cerebral symptoms. Some writers, as Moizard[1] and Lesieur,[2] have said that most of the cases recover. This statement appears to the writer unduly optimistic. If many recover, the opportunity for postmortem evidence is obviously greatly lessened. But the mortality, so far as it is connected with the general pneumonic septicemia, still remains. So that a few autopsies are on record as bearing on the cerebral pathology.

One such case is the following, which I find in the records of the Boston City Hospital, in the service of a colleague now deceased:

G. C., a negro boy, aged thirteen years, entered the hospital December 27, 1883. The mother says he had "brain fever" when young but has been well since except for the past two months, when he has had some headache and has been at times drowsy and forgetful. The present acute illness began four days before he entered the hospital, into which he walked by himself with a temperature of 103.6°.

The symptoms were strongly suggestive of meningitis and such would have been the diagnosis even after the demonstration of a pneumonia.

He cried out with pain, swallowed with difficulty. He slept most of the time at first. The eyes were turned up and to the right. Pupils small, responsive, some lacrimation. He turns mostly to the right side and shows great reluctance at being turned to the left. He moved the left arm and leg much less readily than the right. Tongue protrudes to left; right side of mouth drawn up slightly and the wrinkles are deeper in the right cheek than the left. Loss of sensation in left hand and foot, but sensation increases as one goes up the limbs. Hyperesthetic left side of trunk and face. Patellar reflex absent on left, diminished on right. Plantar reflex much diminished on left, possibly slight rigidity of neck. Short, sharp cries.

[1] Journal de Médecine, lxvii, 889.
[2] Société Médicale des Hôpitaux de Paris, xxviii, 570.

The temperature rose from 103° to 104° and finally just before death to 107.5°.

On the sixth day of his disease he was more irritable, could not bear anyone to touch the bed. There was retraction of the head and stiffness, with flexion of the extremities

The hemiplegia of the left side was less, though there was still partial paralysis of the left side of the face. The right arm resists extension. Many rales were noted in both backs but the diagnosis of pneumonia was apparently not made

In the following week the stupor and irritability increased, there was clonic spasm of the lower jaw and rigid retraction of the head. Finally, he became noisy and incoherent.

This was before the days of lumbar puncture and none was used. But what necessary evidence was lacking of a meningitis? The autopsy, however, gives a surprising contradiction to that view.

It showed the dura everywhere translucent. While the sinus contained considerable blood, partly in soft coagulation, there was no evidence of thrombosis. The vessels of base and fissure of Sylvius were normal.

The pia everywhere was thin and delicate; its meshes contained a very little clear fluid. The lateral ventricles had only enough fluid to moisten their surfaces. The ependyma everywhere was smooth and shining. The brain substance was in general firm, the gray cortex of the usual thickness and "of a dark purplish tint." No tubercles present. The white matter of good color with abundant puncta cruenta. The cord and its membrane were normal.

The lungs showed a chronic adhesive pleurisy, with an acute process on the right pleura, a diffuse purulent bronchitis and an extensive bronchopneumonia of both lungs.

Unless the purplish color of the gray matter and the abundant puncta cruenta of the white may be taken to indicate a slight degree of encephalitis, we have nothing in the section of the brain to explain the marked cerebral symptoms. The death was from the pneumonia and the brain condition which of and by itself would doubtless have been recovered from, seems to have been wholly a toxic affair.

With the foregoing case compare one of Balzer, quoted by Chantemesse,[1] where a patient with aphasia died five days later of pneumonia. The brain was perfectly normal and microscopic examination of the third frontal convolution showed *nil.*

The following case, which I find in the records of Dr. T. M. Rotch, is a rather better marked one of encephalitis, but it gave no such localized symptoms as did the last one, and the patient died without showing any hemiplegia. It seems to support the view of Comby that encephalitis may be associated with pneumococcus meningitis:

An Italian man, aged twenty-two years, had been sick two weeks with a history of fever, cough, and bloody sputum. On entrance there were signs of pneumonia in the right back. The patient made rotary motions with his arms and had frequent muscular twitchings. There was neither paralysis nor strabismus. He became unconscious and died the next day.

The autopsy showed a marked meningitis involving convexity and base with pus about the vessels especially in the commissures and the fissure of Sylvius.

Besides this it was noted that in the right lateral ventricles there were several minute red spots beneath the ependyma representing small extravasations of blood. The whole brain was injected, the puncta cruenta marked. The general color of the brain substance of a pinkish tint.

The following case illustrates a transient aphasia in the course of pneumonia without other paralysis and resulting in complete recovery:

The patient, Edith V., a married woman, aged thirty-one years, had been subject to what were evidently attacks of epilepsy occurring every month. She is said to have been in an insane asylum a year ago. Five days before the present illness she had such an attack and fell to the floor but quickly recovered and returned to work. No specific or alcoholic history. The following day she stayed in bed on account of abdominal pain and general weakness.

She entered the hospital April 8, 1906, with temperature of 104°. Leukocytosis, 22,500. Consolidation right lower back. The next day the speech became unintelligible. Loss of control of bladder and rectum but

[1] Loc. cit.

no hemiplegia. Consciousness intact. Four days later the speech was somewhat clearer but still ataxic aphasia. Two days later the consolidation had increased in the right lung and was present in the left. Five days later it was noted that some words were still imperfectly pronounced but that she did better on a second attempt. She writes well and reads aloud better than she talks. The tongue protrudes slightly to the right; movements of face and of extremities normal. Pupils equal and eye motions normal. Knee-jerks equal and normal.

Four days later, fifteen days after admission, and fourteen after the aphasia, she was talking much better, the lungs were clear. She was up and about and was discharged well.

The most remarkable case which has come under the observation of the writer, of grave cerebral symptoms occurring consecutively to pneumonia and apparently presaging a fatal result, is the following, which was seen in consultation at the Boston State (Insane) Hospital. I have included it in the paper already referred to in the *Medical and Surgical Reports of the Boston City Hospital*, 1913:

The patient, W. M., was an attendant in that institution and a strong and healthy young man of admirable habits.

On February 5, 1912, the patient complained to his friends of headache and general pains. On February 7 he went off duty, and went to bed, complaining of headache and general pains in the shoulders, back, and legs. Constipated. Temperature, 100°. On February 10 his temperature was 104° and he complained of a slight pain in his chest. No sign of pneumonia found. He also had a little cough without expectoration. For the next six days his temperature was irregular, between normal and 101°. On February 16 he had a perfectly normal temperature and said that he was feeling very much better, so that the physician did not see him at all on February 17. On the morning of February 18 he complained of headache and appeared rather dull, answering questions mostly with yes or no. Still no signs of pneumonia were found. When seen at 3 P.M., he showed partial aphasia and partial paralysis of the muscles of the right side of the face, but he was then able to walk and assisted himself while being moved to another room. At 8 P.M. he had complete aphasia and diminished grip in the right hand, but he could move both the right arm and leg and turn over in bed when asked to do so. He understood all that was said to him and coöperated readily with the exception of talking. His temperature at 6 P.M. was 102.4°. At 10.30 P.M. he had a severe attack of propulsive vomiting. I was asked to see the patient on February 19,

when, after getting the foregoing history, the following condition was observed: The patient was dull, saying nothing. He protrudes tongue when requested. Pupils are equal and responsive. No oculomotor paralysis. Right side of the face does not move; right arm is fully paralyzed except for very slight movement of the fingers; paralysis of the right leg nearly complete. Sensation absent on paralyzed side. Complete aphasia. Knee-jerks equal and normal. Is incontinent. Babinski reaction and ankle clonus on right side. Oppenheim and Mendel reaction on right. The heart sounds were clear and there was slight dulness outside the heart apex. No abnormal auscultatory sounds were heard. Respiration was shallow and the patient could not be made to cough or to take a long breath. In view of the septic temperature and the sudden, nearly complete paralysis with its reflex anomalies noted, in a young and previously healthy man, the opinion was expressed that he probably had a septic thrombosis, the infection probably originating in the chest. The blood count which yesterday showed 19,600, was today 13,200, with 93 per cent. of polymorphonuclears. Lumbar puncture brought a clear fluid which was later reported sterile. Widal, negative. Blood culture was also later reported as negative.

February 20. Temperature at 6 A.M. was 102.2° and at 6 P.M. the same. He voided urine and feces in bed, and while he followed the nurses and physician with his eyes, he quite evidently did not know what was going on. However, if asked if his head ached and where it ached, he rubbed his hand over the right side of his head.

Two days later (February 21) I saw him again. The morning temperature was then 104.6°. Pulse, 92. Respiration, 46. The paralysis of the right side was complete. Pain sense absent. No paralysis on left side. He swallows, but with difficulty, and the attempt causes coughing and choking. Says nothing and apparently does not recognize his sister who has arrived from a distance. In the left back where the dulness was found two days ago there are fine rales over limited areas warranting the diagnosis of bronchopneumonia. The prognosis, in view of the worse cerebral condition, was considered highly unfavorable. The event, however, contradicted this prognosis, for after five days of desperate illness, the temperature fell and improvement began. For the remaining as well as the earlier history I am indebted to the careful record of Dr. E. C. Noble who was in charge of the case.

For the next three or four days the temperature remained elevated but in two days he swallowed a little better. On the morning of February 26 the temperature dropped to 99°. He still was incontinent and very restless; aphasia and paralysis complete. Two days later he appeared to recognize the physician and his friends and very slightly moved the fingers of the right hand. No other movement of paralyzed side. Babinski and clonus present on right side. Knee-jerks equal.

March 1, A.M. He slightly moved the right arm but not the foot. In the afternoon he could flex the arm and move the foot a little.

March 3. He spoke for the first time, at 7 o'clock. This was only a muffled sound in reply to someone saying good morning. He said nothing more until 10 P.M., when he distinctly asked, "What time is it?" Temperature normal, incontinent of urine still.

March 4. No longer incontinent. Speech thick. No attempt made to make him talk but he says a few words with effort and seems pleased at doing so.

March 10. Speech has returned, also motions of right side. A slight Babinski and very slight ankle clonus remain.

March 20. Steady improvement during the last ten days. Temperature normal; eating well. Moves unaided from bed to chair. Is dressed for first time.

April 1. Walking outdoors for last seven days and starts for Vermont. No paralysis, aphasia, Babinski, nor clonus. Patellar reflexes equal and normal.

The importance of the phenomena previously discussed is very great from the prognostic point of view and seems to be hardly appreciated.

The diagnosis is sometimes difficult especially from cases of meningitis. Lumbar puncture should always be made to assist the diagnosis. The fluid in meningitis is turbid and may show culturally or by inoculation the pneumococcus, or if the meningococcus, it manifestly removes the case from the category we have been considering. Polynuclear leukocytes predominate in coccus meningitides and lymphocytes in tubercular ones. In encephalitis there is no leukocytosis, and the fluid is clear.

It may be said in passing that the statement of Hoppe-Seiler, Moizard, and others, that the prognosis of pneumococcus meningitis is unqualifiedly bad, is not absolutely true, as Holt[1] has reported a case in which, though the pneumococcus was demonstrated in the fluid removed by lumbar puncture, the patient recovered.

It should also be borne in mind from the meningitis diagnostic point of view that the latter disease may exist especially in alcoholic patients without symptoms. Hoppe-Seiler[2] says that it may occur in old men without stiffness of the neck, vomiting or motor irrita-

[1] Archives of Pediatrics, xxiii, 276.
[2] Lehrbuch der Greisenkrankheiten von Schwalle, 1909, p. 236

tion. In drinkers the symptom may be ascribed to delirium tremens which is really due to a purulent pneumococcic meningitis of the convexity.

In proportion as one can be sure in his exclusion of the organic group of hemiplegias the prognosis is relatively favorable. We still have the pneumonia to reckon with. But if it is true that the cerebral accident does not materially add to the gravity of the pneumonia, one is justified, on the whole, in giving a rather favorable prognosis to such cases, occurring, as they generally do, in young and strong subjects.

DISCUSSION

Dr. J. A. Capps: Is it possible that the changes in the circulation in the brain may be explained as due to reflex disturbances originating in the pleura and occasioned by the pneumonia? Of course, the phenomena may have been due to the toxemia of pneumonia, but very peculiar circulatory effects may follow irritation of the parietal pleura. Russell, of London, has reported reflex circulatory disturbances caused by irritation of the pulmonary nerves; and Lewis and I have done experiments in which with irritation of the parietal pleura, reflex phenomena, even to the production of unconsciousness, have been produced.

But why do none of these disturbances arise in pleurisy?

Dr. Withington: That pneumonia may produce peripheral vascular disturbances is well known, and I had attributed my cases to that cause.

VENOUS BLOOD-PRESSURE AS INFLUENCED BY THE DRUGS EMPLOYED IN CARDIO-VASCULAR THERAPY[1]

By JOSEPH A. CAPPS, M.D.
AND
S. A. MATTHEWS, M.D.
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When one considers the enormous amount of attention that has been directed to the changes in arterial pressure, it appears that the study of the venous pressure has been neglected. There has been no neglect, however, in the study of the waves in the venous pulse. It is fair to say that the investigations of sphygmographic tracings of the venous pulse have thrown as much light on cardiac and circulatory phenomena as have those of tracings of the arterial pulse. Is it not possible that a knowledge of variations in venous pressure may prove as valuable as that of variations in arterial pressure?

Venous pressure has excited the interest of physiologists with special reference to vasomotor influences. It is well known that the arteries of the body are supplied by vasomotor nerves which largely determine the volume and rate of flow of blood within them. Formerly the role of the veins in the circulatory system was looked upon as an essentially passive function. It was assumed that a rise in arterial pressure from any cause is accompanied by a fall in venous pressure, and that a fall in arterial pressure is associated with a rise in venous pressure. Such a conception of the venous pressure is no longer tenable.

[1] This work was done in the Laboratory of Experimental Therapeutics, University of Chicago.

It has been demonstrated by Mall[1] that the portal vein is controlled by constrictor fibers from the splanchnic nerves, and considerable proof has been offered by Roy and Sherrington[2] to show that the systemic veins are also supplied by vasomotor nerves.

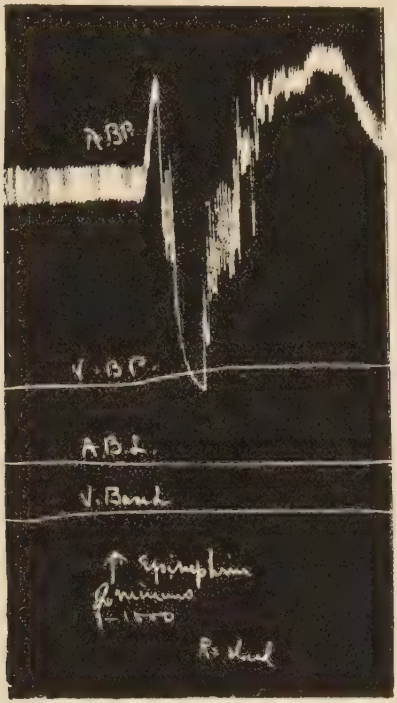

CHART 1.—Tracing to illustrate the rise in venous pressure after a large dose of epinephrin. Note the slow interrupted arterial strokes, showing impairment of heart-action.

Other valuable contributions to our knowledge of venous pressure have been made by Frey,[3] von Basch,[4] Bayliss and Starling,[5] and Sewall.[6] The importance of the subject is indicated by the hypothesis recently advanced by Henderson[7] to explain shock, which

[1] Arch. f. Physiol., 1892, p. 409.
[2] Jour. Physiol., 1890, xi, 85.
[3] Deutsch. Arch. f. klin. Med., 1902, lxxiii, 511.
[4] Wien. med. Presse, 1904, xx, 962.
[5] Jour. Physiol., 1894, xvi, 159.
[6] Experiments on Venous Blood-pressure and its Relation to Arterial Pressure in Man, Jour. Amer. Med. Assoc., Oct. 20, 1906, p. 1279.
[7] Am. Jour. Physiol., 1910, xxvii, 1.

he believes is due to failure neither of the heart nor of the arterial system, but of the venopressor mechanism.

On the clinical side investigations are still meager. Calvert[1] called attention to the value of a rising venous pressure as a danger signal in pleural effusions. Hooker and Eyester[2] carried out a series of observations on venous pressure changes in various diseases of the heart. That the veins, like the arteries, have the power to maintain their blood-pressure within wide limits was emphasized

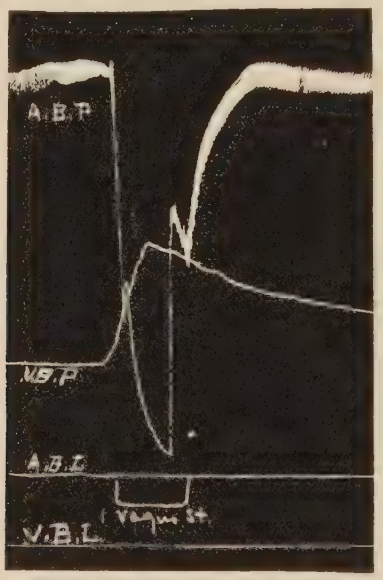

CHART 2.—After electrical stimulation of vagus nerve the arterial pressure falls and the venous pressure rises. Compare with action of epinephrin.

by Moritz and Tabora,[3] who found that it was necessary to withdraw over 500 c.c. of blood by venesection in a human being, before any appreciable fall in the venous pressure occurred. The effect of drugs on venous tension has been very little studied by either pharmacologists or clinicians. The best research of this kind is by Plumier,[4] who in a general survey of the subject records a number of valuable experimental data.

[1] Bull. Johns Hopkins Hosp., February, 1908.
[2] Ibid., 1908, p. 274.
[3] Verhandl. d. Ver. f. inn. Med. zu Berlin, 1909, p. 379.
[4] Etude experimentale des variations de la pression veineuse, thesis, Liége, 1909.

Our experiments were confined to a comparison of the influence of cardiovascular stimulants on venous pressure with that on arterial pressure. Dogs were used and kept under light ether anesthesia during the observations. The venous pressure was taken by the method of Moritz and Tabora, in which a hollow needle is inserted in the femoral vein and the pressure transmitted to a water manometer. A float was devised by Dr. Matthews to carry the delicate

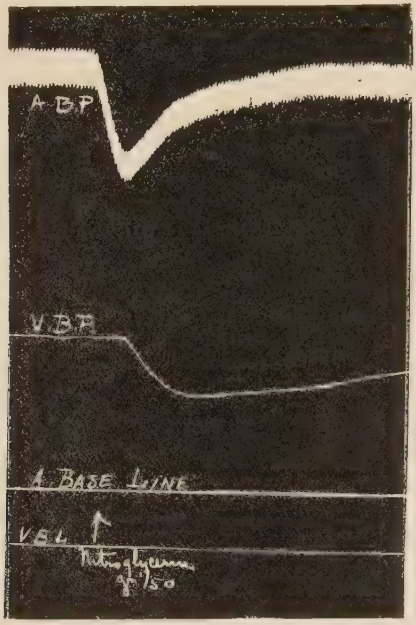

CHART 3.—Following administration of nitroglycerin there is a rapid fall in both venous and arterial pressure, with gradual recovery.

fluctuations of the fluid to a pen, which made tracings on a drum. The arterial tension was recorded from the carotid in the usual manner. The drugs were injected, as a rule, into the femoral vein, opposite to the one from which the pressure was taken.

The Digitalis Group. Three preparations of this group were used intravenously: digitalin in doses of from $\frac{1}{30}$ to $\frac{1}{20}$ grain; digipuratum solution, 1 c.c. (equal to $1\frac{1}{2}$ grains of the powder), and strophanthin from $\frac{1}{120}$ to $\frac{1}{60}$ grain. A moderate and gradual

rise in arterial pressure always ensued. The venous pressure was not materially altered in any instance.

Epinephrin. Doses varying from $\frac{1}{2}$ to 10 minims of a 1 to 1000 solution of epinephrin were employed. This was further diluted in 2 c.c. of normal salt solution and slowly introduced into the

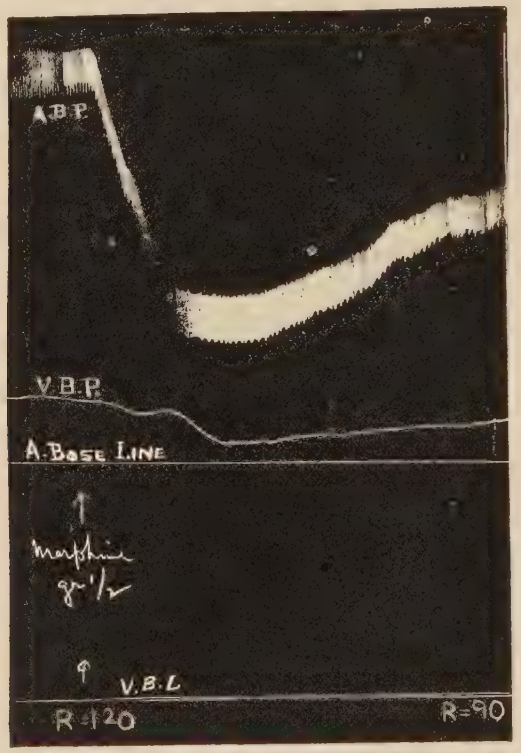

CHART 4.—After large dose of morphine a marked fall in arterial and a moderate fall in venous pressure.

circulation. The arterial tension responded always with a prompt, rapid rise. With a small dose the venous pressure remained the same, but with the larger amounts the venous pressure rose from 10 to 80 mm. A large dose often inhibited the heart-action completely for a few seconds or caused slow, forcible contractions that produced a temporary fall in the arterial curve with slow, long

strokes such as are seen after electrical stimulation of the vagus nerve. Indeed, Cushny[1] considers that the slowing of the heart from epinephrin is due to excitation of the vagus centre in the medulla. The rise in venous pressure was coincident with this halting, irregular action of the heart, and it remained high until the normal rhythm returned. We found likewise that, in the slow or inhibited heart-action from exciting the vagus nerve with the faradic current, the venous pressure rose.

Hence it seems probable, as Plumier states, that the rise in venous pressure after large doses of epinephrin is explained by the halting heart-action rather than by any venomotor stimulation.

Pituitrin (1 c.c. of a 10 per cent. solution). This drug acted similarly to epinephrin on arterial and venous pressures, although the changes were less pronounced.

Caffein. Administered in the form of the benzoate with sodium from $\frac{1}{2}$ to 2 grains, this drug induced a slight increase in the arterial pressure, but did not appreciably influence the venous pressure.

Strychnine Sulphate. This drug affected neither arterial nor venous pressures until the dose was so large as to cause muscular contractions. Under these conditions, of course, the pressure in the veins rapidly rose.

The Nitrites. These, administered by inhalation in the form of amyl nitrite or by injection of nitroglycerin from $\frac{1}{150}$ to $\frac{1}{50}$ grain, caused a decided fall in both arterial and venous pressures. As the heart-action was accelerated and was regular, it does not appear to be concerned in this general lowering of pressure. The drug apparently acts by depressing the nerve endings in the veins as well as in the arteries.

Morphine. In moderate doses of from $\frac{1}{8}$ to $\frac{1}{6}$ grain, morphine tended to lower the arterial tension, without influencing the venous pressure. After large doses, from $\frac{1}{4}$ to $\frac{1}{2}$ grain, the arterial pressure often fell rapidly and the venous pressure also sank to a slight degree. The depressing action of morphine on the venous tension was much less marked than that of nitroglycerin.

Alcohol. Given in strength of from 25 to 30 per cent., from 10 to 50 c.c., the smaller amounts of alcohol depressed somewhat

[1] Pharmacology and Therapeutics, Philadelphia, 1906, ed. 4, p. 460.

the arterial pressure, but did not influence the venous; doses large enough to markedly lower arterial tension resulted in augmenting the venous pressure. It was noted that the rise in venous pressure was proportionate to the degree of disturbance of heart-action.

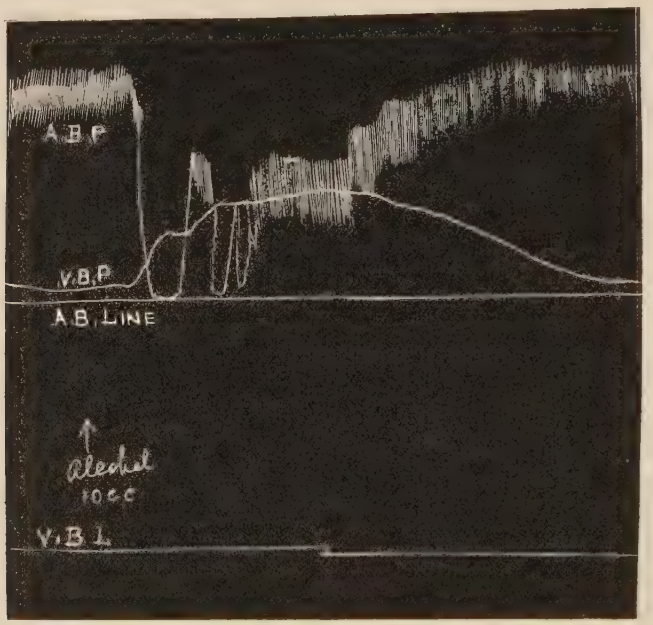

CHART 5.—Excessive doses of alcohol cause a temporary fall in arterial tension and sometimes a rise in venous pressure.

From these observations it is seen that a rise in venous pressure occurred only after large doses of epinephrin, pituitrin, and alcohol. Since in all these experiments the heart-action was seriously impaired, we are justified in explaining the rise of pressure in the veins by the development of stasis rather than by any vasomotor influence.

A fall in venous pressure took place after administration of the nitrites and of large doses of morphine. In these experiments the heart-action was not impaired. Hence the fall in venous tension may be attributed, with a high degree of probability, to a direct influence on the venomotor mechanism.

CIRRHOSIS OF THE LIVER PRODUCED BY CHRONIC PROTEIN INTOXICATION

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THERE have been under observation at the Presbyterian Hospital a few cases of nephritis, characterized by exacerbations of general edema, fever, albuminuria, and occasionally urticaria and eosinophilia, which in these particular attacks have some resemblance to serum disease. The further study of these cases suggested that at least some instances of acute nephritis might have their origin in a mechanism similar to anaphylaxis. The idea, naturally, has been brought forward by others, but as little attempt has been made to study the anatomical changes in tissues from animals that have been subjected to repeated, non-fatal, anaphylactic shocks, a series of experiments was planned to investigate this problem.

Much discussion has arisen as to the manner in which the hypothetical toxic substance anaphylatoxin is formed during the anaphylactic shock, and of late considerable attention has been paid to the analogy between the symptoms and physiological reactions of animals in anaphylaxis and those intoxicated by products of protein digestion. The views formulated by Vaughan,[1] Biedle and Kraus,[2] Friedberger,[3] and Schittenhelm and Weichardt[4] all tend in

[1] Zeit f. Immutätsfsch., 1911, ix, 16, 458; 1911, xi, 673.
[2] Wien. klin. Woch., 1909, xxii, 363.
[3] Friedberger and Goldschmidt, Zeit. f. Immunitätsfsch, 1911, ix, 369; Friedberger and Hortoch, ibid., 1909, iii, 581; Friedberger and Gorber, ibid., 1911, ix, 216; Friedberger and Nathan, ibid., 1911, ix, 567.
[4] Zeit. f. Exp. Path. u. Therapie, 1912, x, 412, 448; xi, 69.

one way or another to explain the phenomenon upon a parenteral splitting of foreign protein and the liberation thereby of toxic substances. According to Vaughan this takes place through the intervention of a ferment within the body cells, while Friedberger upholds the view that specific antibodies are formed for the foreign protein.

As pointed out by Friedmann[1] one question of importance is to determine whether or not the body cells play an active part during the period of sensitization in forming antibodies against the foreign protein, and whether at the time of the shock death comes directly by reason of specific injury to the body cells. Direct proof of the existence of such an antibody in the cells of the organs of animals sensitized to foreign protein is, however, almost entirely lacking (Friedberger, Friedmann), though Fellärder and Kling[2] have stated that antibodies may be demonstrated in the bone-marrow and leukocytes of sensitized animals. Vaughan, however, has dwelt particularly upon the acute injury to the body cells that may take place after the repeated parenteral introduction of foreign protein and has described in rabbits a febrile reaction, together with degenerative changes and hemorrhages in the parenchymatous organs that occur in animals repeatedly inoculated with egg-white. He ascribes these changes to the intracellular digestion of egg-white and liberation of a toxic substance.

Though it seems certain that there is a reaction between the serum of immunized animals and the foreign proteins, it is probably true, too, that a similar reaction may take place between the body cells and the foreign protein. The experiments of Schultz[3] and particularly their amplification by Dale[4] have shown quite definitely that the washed, smooth muscle of the uterus, intestine and bronchi from guinea-pigs sensitized to horse serum will show one of the characteristic reactions of anaphylaxis in the guinea-pig, namely, contraction, when brought in contact with dilutions of horse serum which have no effect upon the muscle of these organs from normal guinea-pigs. It seems probable, therefore, that some of the phe-

[1] Jahresbericht der Immunitätsfsch., 1912, vi, 31.
[2] Zeit. f. Immunitätsfsch., 1912, xv, 409.
[3] Pharm. and Exp. Therap., 1910, i, 549; ii, 221.
[4] Ibid., 1913, iv, 167.

nomena of anaphylaxis, in the guinea-pig, at least, may be dependent upon the direct action of the foreign protein upon the sensitized body cells. Weil[1] has recently discussed this subject and reported experiments upon the anti-anaphylactic states that he believes uphold this view.

The anatomical changes in guinea-pigs dying acutely in anaphylaxis have been studied extensively by Gay and Southard.[2] They describe hemorrhage in the heart muscle, pleura, stomach wall, and cecum, and have called attention particularly to a fatty degeneration of the capillary endothelium which they believe is the direct cause of these hemorrhages. Fatty degeneration was also observed in the nerves, epithelium of the stomach, heart, and voluntary muscle, but Anderson and Rosenau[3] in repeating their work lay but little stress upon the hemorrhages and believe the occasional fatty changes they found may occur in other conditions and are not characteristic of the anaphylactic intoxication. Whether these changes described by Gay and Southard are or are not characteristic of anaphylaxis in the guinea-pig, they occur in my experience quite frequently, though of course the acute emphysema to which Auer and Lewis[4] first called attention is constant. By repeating the shock two or three times in guinea-pigs by intraperitoneal injections Gay and Southard[5] failed to produce chronic changes.

There are, however, in animals reactions to repeated subcutaneous injections of serum in which the body cells participate. The local edema, inflammation, and necrosis that are seen in the skin of a rabbit after subcutaneous inoculation of horse serum repeated at intervals of six or seven days and studied by Arthus[6] is familiar. Gay and Lucus[7] noted the same thing in children receiving repeated injections of diphtheria antitoxin. Another evidence of local reaction is the change described by Friedberger[8] which he produced in the lungs of sensitized guinea-pigs by spraying horse

[1] Jour. of Med. Research, 1913, xxvii, 497.
[2] Ibid., 1907, xvi, 143; 1908, xviii, 407.
[3] Ibid., 1908, xix, 37.
[4] Jour. of Exp. Med., 1910, xii, 151.
[5] Jour. of Med. Research, 1908, xix, 17.
[6] Bull. de la Soc. de Biol., 1903, 817 and 1478; Arch. Internat. de Physiol., 1908, vii, 471.
[7] Jour. of Med. Research, 1909, xx, 251.
[8] Deut. Med. Woch., 1911, No. 1.

serum into the trachea. Ishioka[1] has repeated and confirmed these experiments, while Schlecht and Schwenke[2] have made a careful histological study of the lungs in this condition. They describe a proliferation of the cells lining the alveolar walls and an exudation of eosinophilic leukocytes into the alveoli with the formation of fibrin which gives rise to a type of bronchopneumonia. Moreover, they have studied the effects of repeated intraperitoneal inoculations of horse serum in guinea-pigs as well as the Arthus phenomenon, and find under the circumstances infiltration of the omentum and peritoneal cavity in the one instance and infiltration of the subcutaneous tissues in the other by eosinophilic and small mononuclear cells. Intravenous injections of serum in dogs resulted in an intestinal catarrh with infiltration of the mucosa and submucosa of the intestines by many cells, among which were eosinophiles.

There is, therefore, a certain amount of evidence to show that during anaphylaxis some of the body cells may be injured and a few observations tend to support the idea that the injury may be followed by a reaction on the part of the fixed and migratory body cells.

My own experiments have shown that repeated intravenous injections of foreign protein in animals previously sensitized to that protein give rise to degenerative and subacute inflammatory processes in several organs, and among others the kidney; but it is especially the alteration that takes place in the liver that I wish at present to report. Two former observations have more or less direct bearing upon these observations. Flexner[3] during his work upon toxalbumins noted that in rabbits which had received repeated injections of foreign serum, necroses appeared in the liver which later healed to form scars. Wells[4] has described a cirrhosis of the liver occurring in four rabbits to which he gave repeated doses of peptone intravenously. It is not necessary here to review all the experimental work on cirrhosis of the liver, for this may be found in Opie's[5] work upon the subject and in Fischler's[6] review.

[1] Deut. Arch. f. klin. Med., 1912, cvii, 500. [2] Ibid., cviii, 405.
[3] Medical News, 1894, lxv, 116.
[4] Trans. of Path. Soc., 1903, v, 228. [5] Jour. of Exp. Med., 1910, xii, 367.
[6] Ergeb. d. inner. Med. u. Kinderheilk., 1909, iii, 240.

Methods. For the experimental investigation of this problem it was thought best to make use of several species of animals, and therefore guinea-pigs, rabbits, cats, and dogs were selected. Horse serum and egg-white were chosen as foreign protein. Guinea-pigs were sensitized by the intraperitoneal injection of 0.01 to 0.1 c.c. of horse serum and 0.5 c.c. of undiluted egg-white. In order to render rabbits sensitive much larger and repeated doses were required and consequently two to three doses of the protein were injected at two- to three-day intervals. As a rule, 1 c.c to 3 c.c. were given intravenously, intraperitoneally, subcutaneously, or by a combination of these routes. The cats were injected once with 1 c.c. to 4 c.c. of horse serum or egg-white, either intravenously or subcutaneously. The dogs, depending upon their weight, were usually given 3 c.c. to 5 c.c. of the protein either subcutaneously or intraperitoneally. In some experiments the animals were sensitized both to horse serum and egg-white in order that a single animal might receive the greatest possible number of intoxicating doses.

Twenty to twenty-five days after the preliminary inoculation, the secondary series of injections was started and thereafter injections were made at two- to three-day intervals in some experiments at five- to seven-day intervals in others, and in still a third group at two- to three-week intervals. In the guinea-pigs the intoxicating doses were given intraperitoneally, and the same method as well as an occasional subcutaneous inoculation was used with a few rabbits and cats, but by far the greatest number of rabbits, cats, and dogs received intravenous inoculations. In cats the injections were made into the ear vein, in dogs into the internal jugular or saphenous veins.

It was at first difficult to determine the dose of horse serum or egg-white which would cause definite symptoms without fatal shock and consequently several animals were sacrificed before the proper dosage could be arrived at. Another difficulty that was encountered was the development of an anti-anaphylactic state. This was most rapidly acquired in guinea-pigs. They ceased to show symptoms usually after the second or third intraperitoneal inoculation. Rabbits and cats, however, could be given doses of

horse serum, increasing from 0.1 c.c. to 2 c.c. to 4 c.c. on six or eight separate occasions before they ceased to react, and in the same manner dogs received doses of horse serum up to 10 c.c. before they became insensitive. To large amounts of egg-white the rabbits and cats were never refractory; dogs and guinea-pigs reacted to egg-white as they did to horse serum.

The symptoms following the intoxicating doses in guinea-pigs consisted of scratching at the nose, ruffling of the hair, bucking, defecation and urination, collapse with partial or complete paralysis of the hind legs, with cramp-like convulsions and complete paralysis in several cases. The rabbits showed preliminary excitement, followed by weakness and collapse. The animals flattened their bellies against the floor, lay with their heads back, passed urine and feces, and showed rapid respiration. In the severest shock the rabbits lay upon their sides, occasionally showed spasmodic running movements, or during their muscular contractions flopped about the table. The majority of the animals that reached this stage died. In the acutely fatal cases the animals would run across the floor, then fall on their side, show the running motions, perhaps scream and with bulging eyes and dilated pupils die in extreme spasm with marked opisthotonos.

The cats regularly became excited, raced a short distance, then swayed for a moment and fell upon their sides; immediately there were violent muscular contractions and the animals stiffened out in extreme opisthotonos. After a half-minute to a minute they would relax and lie sprawled out in collapse. Urination, repeated defecation, with bloody movements and occasionally vomiting, would follow. During this time there were contractions of the abdominal muscles, and rapid respiration. After a period of ten to twenty minutes the cats would recover and crawl to a corner where they would sit quietly huddled up for some time.

The dogs after a preliminary short excitement, vomited, urinated, swayed, stood with head hung down, and then lay upon their sides, completely relaxed and collapsed but evidently quite conscious. A diarrhea, often severe, with blood and mucus followed. This condition lasted from ten to thirty minutes, depending upon the severity of the attack. There were spasmodic contractions of the

abdomen. On several occasions severe generalized urticarcia with extreme itching appeared in three days. Though the temperature of these animals was not regularly observed, it was recorded in a few instances and in all cases when definite shock was produced the temperature fell 1° to 1.5° C.

It may, therefore, be seen that these symptoms accord well with the clinical picture of anaphylactic shock as first accurately described for guinea-pigs by Rosenau and Anderson,[1] for rabbits by by Arthus,[2] Friedberger,[3] and Auer;[4] for cats by Schultz,[5] and for dogs by Biedl and Kraus[6] and Pearce and Eisenbrey.[7]

Experiments with Rabbits. Although a total of forty-four rabbits were used in these experiments, it was only possible for several reasons to employ the organs of twenty-four animals for study. The others were discarded on account of the presence of coccidial infection of the liver or other intercurrent infections, such as distemper that might vitiate the results. Of these twenty-four rabbits, twenty-two received repeated injections of foreign protein. Twenty of them, or about 90 per cent. developed changes in the liver. Six of these rabbits were injected with horse serum alone, ten with egg-white alone, five with both substances and one with a 5 per cent. solution of Grübler's casein dissolved in 4 per cent. sodium carbonate solution. No important differences in the histological changes were noted in the different series of rabbits.

The lesions found in the liver were of three types: necrosis, cellular infiltration of the portal spaces, and fibrous overgrowth of the portal connective tissue.

The necroses varied considerably in the different animals, but were present in the majority of cases. They ranged in size from a focus occupied by three to four liver cells, to an area involving about one-third of a liver lobule. They were usually seen in the periportal zone, but might be scattered through the midzone, or even about the central vein. These necroses were most numerous

[1] Hygiene Laboratory Bulletins, 1906, No. 29; 1907, No. 36; 1908, No. 45.
[2] Arch. Internat. de Physiol., 1908, vii, 471; 1910, ix, 156.
[3] Zeisch. f. Immunitätsf., 1911, ix, 216.
[4] Jour. Exper. Med., 1911, xiv, 476.
[5] Jour. Pharm. and Exper. Therap., 1912, iii, 299.
[6] Wien. klin. Woch., 1909, xxii, 363.
[7] Jour. Infect. Dis., 1910, vii, 565.

and largest in animals that died within twenty-four to forty-eight hours after a very severe shock. The following protocol will illustrate such an instance.

Rabbit 26. Weight 1280 grams. Sensitizing doses February 25, 27, and 28, 1913. 0.5 c.c of egg-white undiluted, 1.5 c.c. of egg-white undiluted intravenously and 2 c.c. of egg-white intraperitoneally. March 3, 4, and 5. 2 c.c., 2.5 c.c., and 2.5 c.c. horse serum intravenously.

March 24, 1913. 0.1 c.c. egg-white undiluted intravenously, severe symptoms.

March 26, 1913. 0.1 c.c. egg-white undiluted intravenously, no definite symptoms.

March 27, 1913. 0.2 c.c. egg-white undiluted intravenously, slight symptoms.

April 4, 1913. 0.5 c.c. egg-white undiluted intravenously, severe symptoms.

April 8, 1913. 0.5 c.c. egg-white undiluted intravenously, severe symptoms.

April 14, 1913. 1.0 c.c. egg-white undiluted intravenously, severe symptoms.

March 25, 1913. 0.2 c.c. horse serum intravenously, severe symptoms.

April 7, 1913. 0.5 c.c. horse serum intravenously, slight symptoms.

April 19, 1913. 2 c.c. horse serum intravenously, very severe symptoms.

Death April 21, 1913. Weight 1460 grams.

Lungs show edema and congestion, a little bloody fluid in pleural cavities, heart normal, spleen normal, liver large, firm, brown, surface fairly granular and shows a yellowish reticulated appearance. On section cut surface smooth, but the lobules are lined by delicate yellow lines.

Microscopic examination shows numerous necroses of liver cells, varying in size from two to three cells to ten to twenty cells. The necroses are often seen in the periportal region or in the midzone. The necrotic cells stain uniformly in eosin, they are swollen, the nuclei are lost. There are no cellular infiltrations. The capillaries near the necroses and often between the necrotic cells contain red-blood corpuscles. There are no marked changes in the portal connective tissue.

Similar extensive necroses were found in two other rabbits, both dying after a very severe shock. The cells in these necrotic areas stained deeply in eosin, had a homogeneous appearance, were somewhat swollen and showed a disappearance of nuclei. The capillaries were not occluded by thrombi, but, on the other hand, were often rather wide and contained well-formed red-blood corpuscles.

In other animals that survived several doses of horse serum or egg-white or both, the necroses presented a somewhat different appearance. Here the liver cells were vacuolated, the nuclei piknotic and fragmented and the protoplasm of the cell occasionally contained a mononuclear cell. The stellate cells of Kupffer were prominent in these regions. Such areas were very small, involving only three or four liver cells. In other instances there were foci which showed nothing more than the necrosis of a few liver cells, infiltrated with many mononuclear leukocytes. There were also large, sharply outlined areas of complete necrosis through which one could see evenly distributed elongated, irregular cells, with deeply staining nuclei together, with mononuclear cells. Polymorphonuclear leukocytes were not seen. In still other stages of the process, the large areas of necrosis which lay near the portal spaces were undergoing organization and extending from the portal space into these foci were great numbers of fibroblasts.

The necroses toward the centres of the lobule showed other changes, for in the larger ones a proliferation of the surrounding liver cells could be seen which replaced the necrotic cells and these without scar tissue caused a restitution to normal of the liver substance.

The second type of the lesion was usually present in combination with the areas of necrosis, and consisted in the accumulation of great numbers of small mononuclear cells in the portal connective tissue. They infiltrated these spaces diffusely and often penetrated into the capillaries of the periportal zone, particularly in the region of the necrosis. Together with this infiltration there was a proliferation of fibroblasts forming a loosely woven, sometimes edematous looking mesh-work enclosing the small mononuclear cells. In many animals this produced a slight distortion and irregularity in the shape of the liver lobule.

Rabbit 15. Weight 1415 grams. Sensitization December 31, 1912. January 2 and 3, 1913. 2 c.c., 2 c.c., and 5.5 c.c. of horse serum intravenously. January 6, 7 and 9, 1913. 2 c.c., 2.5 c.c., and 2.5 c.c. of egg-white undiluted intravenously.

January 27, 1913. 1 c.c. of horse serum intravenously, very severe symptoms.

February 6, 1913. 1 c.c. of horse serum intravenously, very severe symptoms.

February 11, 1913. 1 c.c. of horse serum intravenously, very severe symptoms.

January 28, 1913. 0.1 c.c. of egg-white undiluted intravenously, very slight symptoms.

January 30, 1913. 0.4 c.c. of egg-white undiluted intravenously, moderate symptoms.

February 4, 1913. 0.5 c.c. of egg-white intravenously, slight symptoms.

February 7, 1913. 0.5 c.c. of egg-white undiluted intravenously, severe symptoms.

February 12, 1913. 0.5 c.c. of egg-white undiluted intravenously, very severe and death in twenty-seven minutes.

Autopsy. Blood, fluid, heart, and lungs normal; spleen soft. Liver large, dark, fairly firm, with grayish lines about periphery of lobules. Surface smooth. On section cut section slightly irregular showing a net-work of gray lines. Microscopically portal spaces very large and much increase of cellular connective tissue, infiltrated with numbers of small mononuclear cells. Occasionally broad bands of this cellular connective tissue enclose portions of a lobule. There are a few necroses.

The third variety of lesion seen only in the animals that had been inoculated over the longest periods consisted in the replacement of the normal portal spaces by dense fibrous tissue, occasionally enclosing mononuclear cells and forming fibrous bands surrounding partly or completely the lobules. In two rabbits that had been kept for one month after the last injection the portal zone surrounding these fibrous bands contained many regenerating liver cells. In two other rabbits receiving inoculations over a period of four months the increase in portal connective tissue was so marked that it was readily visible macroscopically. The surface of the liver at autopsy was finely granular and on section the cut surface presented a fine mesh-work of gray lines surrounding the lobules. Microscopically these gray lines proved to be old connective tissue replacing the normal portal spaces. The lobules, however, were quite regular in outline.

From a study of many sections from these twenty-two rabbits it seems that the histogenesis of these lesions is as follows: during the injections of foreign protein there occur necroses in the liver

lobule which heal in two ways. The necrosis toward the centre of the lobule show first an infiltration of small mononuclear cells, but later the surrounding liver cells proliferate to take the place of the necrotic cells and finally that portion of the lobule is restored to normal appearance. If the necrosis occurs in the periportal zone, healing takes place, at least in part, by scar formation, the fibroblasts wandering out from the portal connective tissue, and finally the necrotic area is incorporated in the portal space, giving rise to a temporary distortion of the lobule. With the continued production of this process the portal spaces gradually replace parts of the periphery of the lobule and become thick.

Before discussing the possible interpretation of these changes I will state the results of experiments upon the other groups of animals.

Nine cats were sensitized and inoculated in the same way as the rabbits; of these four showed changes in the liver similar to those described for the rabbits, though they were not as pronounced. Two cats which received two intoxicating doses of egg-white showed a few necroses infiltrated with small round cells in the periportal zone together with a slight increase of portal connective tissue which was infiltrated with small round cells. One cat receiving twelve intoxicating doses of egg-white showed much the same microscopic changes in the liver. In the fourth cat the lesions were most marked. The protocol of this experiment follows:

Cat 3. Weight 3000 grams. Black and white. Sensitized November 19, 1912. 5 c.c. horse serum intravenously; January 6, 1913, 4.5 c.c. egg-white intraperitoneally.

December 27, 1912. 4 c.c. horse serum intraperitoneally, no symptoms.
January 6, 1913. 0.25 c.c. horse serum intravenously, severe symptoms.
January 8, 1913. 1.5 c.c. horse serum subcutaneously, localized edema.
January 11, 1913. 4 c.c. horse serum intramuscularly, slight symptoms.
January 13, 1913. 7 c.c. horse serum intraperitoneally, severe symptoms.
January 15, 1913. 10 c.c. horse serum intraperitoneally, no symptoms.
January 16, 1913. 3 c.c. horse serum intravenously, slight symptoms.
January 18, 1913. 4 c.c. horse serum intravenously, slight symptoms.
January 22, 1913. 5 c.c. horse serum intravenously, slight symptoms.
January 24, 1913. 6 c.c. horse serum intravenously, no symptoms.

January 27, 1913. 0.25 c.c. egg-white intravenously, moderate symptoms.

January 31, 1913. 0.6 c.c. egg-white intravenously, severe symptoms.

February 4, 1913. 0.8 c.c. egg-white intravenously, severe symptoms.

February 7, 1913. 1 c.c. egg-white intravenously, severe symptoms.

February 12, 1913. 1 c.c. egg-white intravenously, severe symptoms.

February 12, 1913. 2.5 c.c. egg-white intravenously, continues ill.

Died during night of February 12, 1913; passed bloody urine.

Autopsy. February 13, 1913. Hemorrhage in epicardium and endocardium. Lungs normal. Spleen large and soft, kidneys, pancreas, stomach, and adrenals normal. Intestines contain bloody mucus and show congestion. Liver yellowish, smooth, rather firm, regular. On section cut surface smooth, yellowish, cloudy. Microscopically liver cells cloudy and contain fat droplets. Portal connective tissue is much increased, forming a zone about most of lobules. It is infiltrated with numbers of round cells.

In this instance one might fairly speak of the condition as a moderate portal cirrhosis. This animal, too, received the greatest number of intoxicating doses of protein and in the largest quantity.

The cats that showed normal livers at autopsy received respectively three and six doses of horse serum intravenously, eleven doses of horse serum intraperitoneally, nine doses of egg-white intravenously, and four doses of egg-white combined with four doses of horse serum intravenously. Though the cats showed liver changes less frequently and in milder degree than the rabbits, the changes were of the same kind and must be interpreted in the same manner.

On the other hand in none of the dogs or guinea-pigs were there significant changes in the liver. Two of eighteen guinea-pigs showed slight increase of portal connective tissue, and one periportal infiltration by eosinophilic cells, but it is not possible to attach any significance to these observations.

The question arose as to the exact significance of the alterations in the livers of the rabbits and cats. The possibility was, of course, kept in mind that these might be spontaneous lesions. In the rabbit infected with coccidia a mild or even marked grade of cirrhosis is not uncommon, but Saltykow[1] states that except for the changes associated with coccidiosis, spontaneous cirrhosis in

[1] Cent. f. allg. Path. u. path. Anat., 1911, xxii, 849.

the rabbit is exceedingly rare. Ophüls,[1] however, who has examined the livers of fifty supposedly normal rabbits, found only six with absolutely normal livers. The remainder showed coccidiosis, and occasionally cirrhosis was encountered in rabbits in which coccidia could not be found. In the study of the livers from a series of twenty-five control rabbits we have had much the same experience. In practically all cases where coccidia were present, more or less increase in portal connective tissue was observed.

In the rabbits that I have used for these experiments all animals with coccidiosis have been excluded, in order to eliminate this factor. The necroses, too, which were so constantly present in the animals subjected to experiment I have not observed in any uninoculated animals. Again it was possible to follow the development of the lesions through a series of rabbits from the normal control to the liver with necrosis and finally cirrhosis.

Rabbits 25, 26, and 27 sensitized at the same time and in the same way to egg-white and horse serum.

Rabbits 28, 29 and 30 sensitized at the same time and in the same way to egg-white alone.

Rabbit 28 killed as control on third sensitized dose, liver normal.

Rabbit 29 received nine intoxicating doses of egg-albumen over a period of twenty-six days. Liver showed extreme fresh necrosis. No change in portal spaces.

Rabbit 30 received ten intoxicating doses of egg-white period of thirty-two days. Liver presented many necroses, some of which showed invasion by connective tissue.

Rabbit 26 received six intoxicating doses of egg-white and three of horse serum over period of twenty-six days. Liver showed numerous necroses, slight changes in portal connective tissue.

Rabbit 25 received eleven intoxicating doses of egg-white and nine of horse serum over a period of seventy days. Liver shows old healing necrosis with marked cirrhosis in rather dense connective tissue in portal spaces, with infiltration of small round cells.

Rabbit 27 kept as control. No intoxicating doses. Killed seventy days after sensitization. Liver shows few necroses with some increase in portal connective tissue.

In such a series one may exclude almost certainly the possibility of confusing these alterations in the rabbit liver with spontaneous

[1] Proceedings of Soc. of Exp. Biol. and Med., 1911, viii, 75.

lesions. In the cat the danger is very slight for I have examined the livers of fifteen normal cats without observing any abnormalities. Moreover these alterations are not confined to the liver. In rabbits and dogs I have observed necrosis of the cells of the kidney tubules with surrounding inflammatory changes, while all groups of animals have shown small foci of necrosis in the myocardium much like those seen in the liver of rabbits and occasionally an extensive myocarditis has been observed. Some of the experiments of Schlect and Schwenke have also been repeated in rabbits, guinea-pigs, and cats, and after repeated intraperitoneal injections of egg-white or horse serum the omentum and peritoneum are found to be thickened and to show, on microscopic examination, chronic inflammatory changes.

It has seemed to me probable therefore that the changes in the liver represent a single conspicuous manifestation of a somewhat generalized cell degeneration and necrosis together with a reaction on the part of the body which takes place when foreign protein is repeatedly introduced parenterally.

A question which is difficult of solution is the exact cause of this destruction and reaction of the body cells. Is it produced entirely by the repetition of the anaphylactic shocks, being dependent for its origin upon the hypersensitiveness of the animals to the foreign protein, or is it merely due to some alteration brought about in the tissues irrespective of the hypersensitiveness of the animal, whenever a single injection of foreign protein is made?

It is known that foreign sera may in themselves be toxic and it has been shown by Uhlenhuth,[1] Pfeiffer,[2] and by Kusama[3] that animals inoculated with certain heterologous sera may develop necrosis of the skin, or if the sera are given intravenously, necrosis of the liver. These necroses are obtained only with sera that are hemolytic for the blood of the inoculated animals and the necroses have been shown to be dependent upon the formation of capillary thrombi, often formed of agglutinated red-blood cells. Pearce,[4] too, has observed extensive central necroses in the livers of dogs

[1] Zeit. f. Hyg., 1897, xxvi, 384.
[2] Ibid., 1905, li, 183.
[3] Ziegler, Beiträg., 1913, lv, 459.
[4] Med. Research, 1904, xii, 329; 1906, xiv, 541; Jour. of Exp. Med., 1906, viii, 64.

injected with artificially prepared hemolytic or hemo-agglutinative sera and has traced the cause of the necrosis to capillary thrombi.

Such an explanation does not hold, for the lesions observed in these experiments for capillary thrombi could not be discovered in or near the liver necrosis. It is evident, however, that egg-white, as Vaughan has shown, is itself toxic for rabbits and in a few instances lesions have been found in the livers of animals that had received only the sensitizing doses of this substance. In rabbit 27 definite old changes were seen in the liver seventy days after three sensitizing doses of horse serum given intravenously and three of egg-white, two of which were given intravenously and one intraperitoneally. On the other hand, in rabbit 28, that died immediately after the third sensitizing dose, the liver was normal, and in rabbits 1, 23, 100, and 101, all of which died from the second and third intoxicating dose of egg-white, the livers showed extremely slight changes.

If the alteration that I have described were dependent solely upon the primary toxicity of the protein, one would expect to find the most extreme stage of the process soon after the sensitizing doses were given for the amount of material introduced at this time is enormous as compared with the quantity introduced during the production of the anaphylactic shock. But it is during this later period and not immediately after sensitization that the lesions in the vast majority of the animals are first seen. I am therefore disposed to believe that the slight primary toxicity of horse serum and egg-white for the liver of the cat and rabbit is greatly enhanced through primary injections or sensitization of the animal for these substances.

Whether or not the cellular necrosis, which I believe is the primary injury, and upon which develops a chronic inflammatory process, is due to a toxic substance liberated during the anaphylactic shock in the blood stream, or whether it is due to the liberation of a toxin within the cell protoplasm by the action of an antibody, or possibly digestive ferment upon the foreign protein parenterally introduced, these experiments cannot decide, though it might be possible to plan experiments to elucidate this point.

Conclusions. The repeated parenteral introduction of foreign protein into sensitized rabbits and cats with the production of repeated anaphylactic shocks gives rise to destruction of the cells of several organs with subsequent chronic inflammatory process about the necrotic foci.

The necroses are well marked in the liver and are often seen in the periportal zone.

A chronic inflammatory process follows and the result of the destruction of the liver cells and chronic inflammation is an increase in the portal connective tissue. This in advanced cases produces a picture which is analogous to the portal type of cirrhosis of the liver.

ON CERTAIN OF THE BROADER ISSUES OF THE PSYCHOANALYTIC MOVEMENT

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In bringing forward for discussion, at this time and place, some of the more important practical considerations and scientific principles underlying the psychoanalytic movement, I have been moved by the belief, carefully formed and confidently held, that this movement, capable of contributing, as it is, to the health and happiness of vast numbers of men and women; and essential, as it has shown itself to be, to the thorough study of character formation, of the psychology of childhood (and so of education), of mythology, etymology, and, indirectly, of religion, marks one of the most important advances of modern medicine. It may need modification and supplementation and safeguarding, but it cannot be ignored, and must be fostered, not by neurologists alone but by physicians of all sorts, to whom neurotic patients constantly apply for a relief which they cannot adequately give. It should be seen to be entirely wrong, now that the causal mechanism of these numerous and disabling psychoneuroses is so clearly understood, that physicians and patients should go on laying the chief emphasis, in explanation and treatment, on incidental disorders of some special organ or on some abnormality of nutrition, provided the chance is at hand of getting nearer to conditions which are far more fundamental. Various circumstances may compel the ignoring of these conditions, it is true, in given cases, but this should be done with the eyes open and will become less often necessary when more men of high standing have been encouraged to take up this work.

This method of treatment is not simply one more means of palliation. It is based on a recognition of the fact that these patients are suffering from emotional conflicts the nature of which

they cannot understand unaided, and is an attempt to make it possible for them to extricate themselves, through self-knowledge and self-education, from the effects of these conflicts. It is not, furthermore, in its essence, a method which is dependent for its success on some unmeasured and subtle personal magnetism on the physician's part. On the contrary, it is a *system* which anyone can learn who is willing to take the great amount of pains needed for this task. As a part of this system, the personal reactions of patient and physician on each other are made the subject of careful scrutiny, and subjected to constant control.

Care should be taken to distinguish sharply between the merits of the *method as such*, and the mode of its application in particular cases. Many physicians approve of the former, who think there is reason to criticise the latter, and such physicians owe it to their patients to test the correctness of this attitude. No one doubts as to the importance of a thorough anamnesis as the basis of a thorough treatment, and every student of human nature is aware that a man who is struggling with internal problems and resistances is in no shape to meet and solve external problems. But the very aim and object of this method is the securing of a thorough anamnesis, and the bringing home to each patient, in a form which admits of no misunderstanding, not only of an intellectual sort but of any sort, the real nature of the conflicts through which he passed in childhood and is passing. These internal conflicts form the natural problems in terms of which every growing child ought to build his rational and moral character, and a psychoanalytic treatment is a form of rational and moral education.

The results of the conflicts of our childhood do not die and disappear. On the contrary, they live forever, in an active form, and continue to produce effects, either as integral forces, interwoven with the living fabric of our temperaments and characters, determinants of our thoughts and conduct, or else as hostile elements to be continuously reckoned with. It is, therefore, difficult to see how the student of education could fail to welcome any new means of rendering these conflicts clear and bringing them face to face with the intelligence and the moral sense.

It is often asked, "Of what benefit is it to make the patient

intellectually aware of these long since repressed and forgotten problems and frailties of his youth?" "Simply to *see* the terms and bearings even of a present temptation or perplexity is not equivalent to overcoming the one or solving the other; and as for bygone temptations and perplexities, once inadequately met and solved, to be forced to re-discover them is to be made painfully aware of weaknesses which would better be forgotten and ignored. Repression is useful as well as harmful; it is a means of progress which was instinctively arrived at and found practically useful." Such is the general character of the argument.

But, in fact, although the intellectual presentation of the bearings and nature of a present perplexity or temptation is not in itself equivalent to a moral or a rational victory, yet to arrive at such a presentation for one's self, with or without aid, is the first step toward the victory, *if the person tempted or in doubt really intends to make it such,* and if he does not intend this, the nature and reason of his unwillingness should become the next object of his search. But what is true, in this respect, of present conflicts is true of old conflicts. For the latter still exist, and form, in reality, the main basis of the former, and the argument itself is only one of the many instinctive resistances to the forces working for change and recovery, resistances that are built up as defences to preserve a *status quo* of invalidism which, though unsatisfactory, has become sacred because it serves for the maintenance of old memories and experiences (painful yet pleasurable) which had been repressed but still exists as hidden cravings.

As for the assumed usefulness of "repression," the true explanation of this paradox was hinted at in the last sentence. Repression, is a word, like so many more, of double or multiple meaning. It is a good thing to repress, on rational or moral grounds, the desire to yield to a temptation which one clearly sees. It is a poor thing to turn one's back on a temptation which one does not wish to see or reckon with, deluding thereby one's companions or one's self with the idea that the tendency to the temptation has been overcome, while in reality this tendency is preserved as a source of illicit and harmful pleasure, to be continuously played with though not under its own name. It is this latter sort of "repression"

which is characteristic of childhood, or of common occurrence in childhood, and the accuracy of the statement which I have made with regard to the frequent outcome of it is vouched for by the very fact of the occurrence, later, of nervous symptoms, or defects of character, which, under an adequate inspection of their thoughts, the patients themselves trace clearly to the mechanism outlined. As regards the persons—few in number and sure to become less numerous as the skill of their physicians becomes greater—who seem to get harm from self-analysis of their past conflicts, the causes of this ill result are classifiable for the most part under two categories: (1) lack of thoroughness or of adequate opportunity on the physician's part; (2) an instinctive clinging to his illness on the patient's part—a clinging based on the unexpressed feeling that the illness, unpleasant though it be in some respects, secures a better equilibrium and greater freedom from discomforts than any substitute which appears to be in sight. All these facts and conflicts the patient may, if willing and if reasonable, be helped to see, and in seeing them he penetrates, loosens up, and in favorable cases forces to disappear, the incrustations of habit and unconscious craving which had made his will a prisoner, much as the sun of February and March makes soft and porous, even without at first altering its external aspect, the ice in which river and pond had been imprisoned.

These statements may serve as an introduction to the next proposition, which has reference to the difficulties which the physician must encounter in fitting himself for adequately carrying out the psychoanalytic treatment. Except for these very real difficulties, the records of more frequent and thorough tests of the method and a greater number of critical comments (favorable or otherwise) based on personal experience, would doubtless have appeared.

It is now nearly four years that I have been laboring to make really my own the principles and practice of psychoanalysis, yet at the same time keeping clearly in sight, and striving to grasp and to feel the full influence of the great scheme of human development in obedience to which all education, including that by psychoanalysis, must unfold its powers. I have learned, through con-

stantly renewed efforts, disappointments, and successes, that while it is easy to penetrate, to a certain extent, beneath the disguises of the conventional and habitual modes of thought of any given patient, and to enable him to do the same, it is often very difficult to utilize effectively the knowledge thus gained, so as to bring about the disappearance of symptoms in difficult cases, or to see where the causes of failure lie, or, finally, to satisfy one's self that the progress made is sufficiently in the line of the best final progress ("sublimation" in the best sense).

While, then, the first point that needs ever renewed emphasis is that through this treatment, as through no other to anything like the same extent, patients suffering hopelessly from obsessions, morbid fears, and kindred symptoms can almost always be enabled to see and often entirely to overcome their troubles, the next point is that the task, though full of interest for both patient and physician, is not a light one. Any intelligent, careful person may utilize to some extent the principles worked out by the leaders of this movement, and may, through prudence and caution, avoid exciting in the patient, in any serious degree, the sense of dependence on the physician ("Uebertragung") which has so often proved a formidable objection to every kind of mental therapy; yet it is a very different affair to carry through really difficult cases to a successful issue.

Fortunately, the student of the future will have the great help of the papers of practical advice which Freud has published during the past year, and will, it is to be hoped, long continue to publish. A careful reading of these admirable commentaries would make it clear to anyone that it is not alone a theoretical knowledge of the psychology of the "unconscious," on the physician's part, not alone technical skill, that is necessary for success, but that there is need also of self-restraint, patience, sincerity, an inflexible confidence in the ability of the patient to reveal himself, to his own advantage, if his will to do so goes deep enough, and the thorough-going adoption of the principle that no considerations of temporary satisfaction, on the part of patient or physician, should be allowed to override the main issues of the treatment, but that, on the contrary, both patient and physician should

recognize from the outset that the task before them may call for material sacrifices on both sides.

It has, indeed, come to be recognized more and more by the leaders of this remarkable movement, that one prominent cause of disappointment is the existence of defects or peculiarities of character and temperament on the physician's part, which blur the mental image that he seeks to form of the real patient, and unfit him for developing the patient's own powers as he might otherwise have been able to do. The discovery of these defects makes one realize the significance of Hans Andersen's story of the distortion mirror, which the evil sprite shivered into a million fragments, that found lodgement in the eyes and hearts of his unwary victims, causing them to see everything awry. Few persons are so well endowed by nature as to be free from the liability to get these distorted images, and it is now looked upon as very important, and indeed almost essential, that the psychoanalyst should himself have been through the same sort of self-examination, under the supervision of some expert, that he proposes to make use of for his patients. With such thoroughness in preparation presupposed, this field of work is certain to become more and more attractive to men of the best stamp. If the noblest study of mankind is man, then surely the experiences of the psychoanalyst, who sees the internal conflicts of human beings at peculiarly close range, should call out the very best qualities that he is capable of exhibiting.

Considerations of this sort should appeal preëminently to general practitioners of the best stamp, such as those who make up this body of representative physicians, and should go far toward establishing on a firm footing the opinion that the psychoanalytic movement, *at its best*, so far from tending to encourage lower ethical standards on the part of the physician, the patient, or the community, is certain to exert the opposite tendency. For choice implies conflict, and every conflict implies an antagonistic action of two interests, one of which is likely to be more in the line of the best sort of progress than the other. It is true that the progress which a patient makes in getting well is not necessarily of a very high sort, since the forces represented in some of our human con-

flicts may be between tendencies both of which might be characterized as relatively selfish. But, on the other hand, issues necessarily present themselves in the course of every psychoanalytic treatment, which have to be met through the exercise of qualities of a better sort than those that had previously been most prominently in play; and this must redound to the moral stimulation, as well of the physician as of the patient. In fact, the moral influence of the treatment often goes very much beyond this minimum in the direction of "sublimation." Psychoanalysis was primarily introduced, it is true, solely as a means of ascertaining the contents and influence of those tendencies in our lives of which it can be said, not only that they lie outside of consciousness, but that they are under the ban of "repression," and yet remain as objects of unconscious desire or craving. To render a person clearly aware of such tendencies as these is the first step toward making it possible for him to modify them and utilize them for good; and the task of the psychoanalyst has usually been considered to cease with the accomplishment of this first step.

The reasons for not going farther and studying the *quasi*-repressions such as impede the best development of the moral nature have, however, been reasons of a purely practical character. The distinctive task of the psychoanalyst is so difficult, and calls for an expert training and a scientific attitude of such special sorts, that no one could do his profession or his patients justice, it has been felt, without devoting himself exclusively to the problems coming before him as a scientific expert. If he attempted more, even if qualified to do so, he might perhaps accomplish less.

I do not myself believe, however, that this view is altogether sound, or should be considered binding. Psychoanalysis is, after all, a phase of education, and has been characterized as such by Freud. Education is of different sorts, but the goal of every kind of education is in a measure determined by the nature of the human mind, and the psychoanalyst of the future is likely to profit greatly through the recognition of this fact. This movement cannot steer its difficult course or accomplish its whole mission under the exclusive guidance either of biogenetic methods or of those principles which the students of the processes of inorganic nature have worked

out for their particular needs, and have so often and so erroneously assumed to be final statements of the truth. For these principles do not by any means explain the working of the mind, nor account *for the origin* of the instincts or tropisms or the chemical phenomena which are supposed to foreshadow mental action; and, moreover, they turn aside the attention from other principles which refer mind, instincts, and chemical processes alike to the influence of a self-renewing, self-active energy seeking fuller and fuller opportunities for self-expression.

I cannot pursue this argument further here, but assert, as my opinion, that the study of the vitally important relationship between the life of the individual and the total life of the universe (which embraces that of the individual yet leaves him independent), and the adequate study of the laws of mental action, will afford a basis, of a much needed sort, for the understanding of the true place of the psychoanalytic phase of education on the great scheme of psychologic evolution. It may well be that among the qualifications considered essential for the psychoanalyst of the future, certain sorts of training which are now thought little of will be included. Certainly the only logical stopping place of a complete psychoanalytic treatment is a complete "sublimation."

The psychoanalyst must indeed be a scientific expert, eager to see his special art advanced, and this need must be considered paramount to every other. But in every department of learning there are men whose powers best fit them for the exclusive study of some special problem, and others who do better service, even in detail, if they see each special problem on the background of a comprehensive scheme. Fortunately for the advancement and ultimate welfare of the psychoanalytic movement, a number of men of this latter type have already enlisted for the campaign, and the leader of the whole enterprise is a man of constantly widening views.

It will have been guessed at from the trend of the foregoing statements, even if not already known, that the main emphasis of a psychoanalytic investigation and treatment has gradually been shifting more and more, toward the mysterious, the apparently, but not really forgotten years of childhood, that period which is more

important than any other, for the formation of character and temperament. Strictly speaking, it is not alone childhood as a whole, but especially the earliest years of childhood, including infancy, from and embracing the experience of birth itself, of which these statements can be made.

In what terms can one best express the nature and bearings of the conflicts with which the young child finds himself confronted; and in accordance with what principles does psychoanalysis attempt to neutralize the ill results that often flow from his instinctive efforts to find a solution of these conflicts, in the form of some compromise that shall satisfy, after a fashion, the demands of both his lower (less evolved) and his higher nature?

What one seems to see in making a thorough psychoanalytic investigation is that specific influences occur at more or less definite epochs in the development of every child (of some far more than others), which are so strong that they are able to overcome to a greater or less extent the expansive forces tending toward further progress, and thus to cause a partial "fixation" of his emotional interests or partial "arrest" of his psychological evolution.

If we assume, as we may, that every child, like every person still capable of development, is continually subjected to the action of two forces, one of which tempts him to follow the broad path of ease and pleasure, and the life of fancy, the other the straight and narrow path tending toward a better understanding of the meaning of conscience and reason and of the stern realities of the world, we may admit that the "fixations" or "arrests" to which I have referred take place in the interest of the former of these two forces. The child then accustoms himself, for the time being, to the abandonment of his best outlook, and learns to content himself with aims less good than the best. Emerson's striking poem, "The Days," is a good illustration of this principle. The principle itself is indeed a familiar one; but the merit of Freud and his followers consists in the detailed demonstration of the special phases of childhood with reference to which the arrests occur, and also in showing how the reactions of the individual in later years of life (including his vocational tendencies) are determined, in great measure, by these reactions of his very earliest years.

These phases of childhood include: (1) the period in which the child, occupied mainly with the differentiation of himself from the world about him, learns to observe, assimilate, and classify the increasing number of sensations having reference to his own person (his bodily functions, excretions, and hunger reactions); (2) that in which this autosensuous tendency assumes a more elaborately egoistic form, which, when developed to a distinctly morbid extent, is characterized by the term "narcissism;" and (3) the period in which the child, filled with the wine of his newly found capacity for egoistic pleasures, comes in contact with his parents, and learns to take them as objects for an emotion which is partly fine and unselfish, but partly also, and often very, selfish in its type, as is also, in part, the affection of the parents for the child.

Throughout these periods, and those that follow, the child is exposed to influences from the side of his environment, not all of which are put definitely into words, or even signs, through which he learns to find himself approved or disapproved, in whole or part. In the beginning it is approval that predominates, and so much so that the child often learns, as a result of the devoted care of his parents, and for other reasons that cannot here be fully stated, to feel himself all powerful as regards the gratification of his wishes. Then, however, as from the beginning in some measure, comes the necessity of sacrifice, and the tendency to seek compensation for sacrifice in the form of fantasies of wish fulfilment.

Psychiatrists are familiar with the extraordinary archaic and apparently meaningless reveries of patients with dementia precox, in the course of which fantasies of the wildest sort find currency. This sort of mental life of compensatory fantasy has been termed by Bleuler "autistic" thinking; and there is good reason to believe that if we could probe sufficiently far the memories of any child we should find that such wild, seeming thoughts had formed, at some period, a portion of his mental furniture. It would be of enormous service to the child if its parents and teachers were able to understand and sympathize, even in some measure, with these crude fantasies, and to realize that they were acting as a means for the expression of valid conceptions of great moment.

The tendency to a relative reversion toward this autistic state

is a tendency of immense strength, and its influence may modify the further progress of the individual. In seeking some graphic illustration for the strength of this tendency, my mind has many times reverted to the analogy of the formation of the animal species during the course of evolution.

It would be absurd to push too far this analogy between the case of the partially arrested child, who may perhaps retain the power of absolute recovery, and the arrests characteristic of the different animal species. It is fair, on the other hand, to note that in both cases the path of development which leads toward the higher sorts of spiritual progress is very slender and hard to follow, as compared with the paths which lead toward ease and comfort—or, in general, toward results which are of use only in and for themselves, and not as avenues toward a better goal. When the case presents itself of helping a patient to recovery in whom these tendencies have become established, it is of great service to him not alone to see clearly the better path toward reality in the widest sense, but to put himself back again in memory and imagination at the point where the first occurred, in order that he may see clearly what a different choice at that moment would have accomplished for him, and that he may now make it, as if for the first time. For these problems must be conceived in psychological terms. We must see each individual as a collection of interwoven forces, all living and still active, even though many of them came into existence in the early days of childhood. And one who does not possess by nature, or cannot acquire the power of thus reading the lives of his patients in the terms of these living forces is not at all likely to find satisfaction or success in psychoanalytic practice.

Finally, I beg leave to call your attention to a picturesque and simple illustration of the fact that neurotic symptoms, as they finally appear (by virtue of being compromises which contain something of the repressed pleasures which the child fancies himself to have abandoned, and something also of the desire for better things for the sake of which the sacrifice was made) differ from both sets of causes which gave rise to them. What information can a person who is afraid to ride in a street car derive as to

the cause of this fear from a never-so-careful study of the conditions relating to the car itself? And what hint at the real conflict which was formerly at stake can a patient obtain through direct contemplation of the obsession that some act of his will destroy the life of some person who stands near to him? Let anyone take a sheet of note paper and draw a flame toward one side, a cross toward the other, and a line of division between them. In this diagram the flame may stand for the emotions and fantasies of childhood, such as every child loves to play with, even when they get so hot as in some degree to burn him. Imagine that the time arrives, however, when this burning becomes too strong, and fear or distress (the fear of himself, his own emotions) takes, almost entirely, the place of pleasure. Then the child is led to seek some explanation of his distress, which he dislikes and does not clearly understand. To use Dr. Ernest Jones' term, he instinctively seeks to "rationalize" his distresses. This he does by inventing this or that situation, as in the instances cited (fear of street car, etc.), which he may artificially clothe with the trappings of his feelings of apprehension. In this way the cross is built up, which primarily represents what in popular language is called "a cross"—that is, a collection of disagreeable memories, experiences, or fears. The psychoneurotic fears and impulsions are, in a sense, artificial—that is, they stand for the real, original fears, but do not actually represent them.

If now the patient would recover, and cannot do so through the interest of work or by the attempt to get into a spiritual atmosphere above the fear, he must learn to turn his attention wholly aside from the cross, the contemplation of which he is certain to have followed too long and to too little purpose, and must study the flame—that is, he must study the history of his emotional life. An intimate acquaintance with this history, by teaching him the real nature and origin of his fears, and showing them to be fears of himself, puts the patient in a far better position for attaining that development of character through which, after facing out his own temptations, he may get well. Then the cross in the old sense disappears, although it may be replaced by the cross in the sense of the Christian symbol—as representing the willingness to

endure sufferings, not indeed of the sort he formerly endured, but of a sort which will make him better able to take his place as a useful member of the community. The person who has attained this development has learned, in Emerson's words, that "when half-gods go the gods arrive"—the half-gods being his own immature desires. What every person wants is happiness and content. But these are to be gained, as a rule, not through seeking for obvious pleasures, but rather through disregarding them in the interests of growth, development, and disinterested love.

As a contrast to this disinterested love, which seeks really to promote the welfare of its object—that is, to give itself really to its object—the egoistic love above referred to may be thought of, in which the individual uses the object of his affection as a means of intensifying his own admiration of himself, and accentuating the pleasurable excitement of love in and for itself. This is the sort of love which is called out by the "love philtre," which makes its recipient take the first person, whoever he may be, as the object of his affection, and which, in the case of Titania, is seen carried to a ludicrous development.

To sum up: psychoanalysis (including the marvellous dream analyses), if looked at *as a method*, is a development of scientific genius; it is bound to become as indispensable to the student of human life as a microscope to the anatomist and pathologist of the brain.

If, now, inquiry is made as to the practical outcome of the use of this method, the answer may be made that only the wilfully blind could deny that by means of it thousands of men and women, hitherto tortured with the misery and terror of fears, doubts, compulsions, and the sense of isolation from their neighbors and themselves, the causes of which they did not and could not know, have found permanent relief, and that a *system* has been placed at the disposal of all who wish to avail themselves of it, through which these benefits can be indefinitely extended.

It is no longer a question whether, in the face of the enormous difficulties of the practical situation by which the psychoanalyst is confronted, an occasional patient—unwisely, unskilfully, or incompletely treated it may be—gives voice to complaints, irrita-

tion or regrets; but rather whether for each such patient it would not be easy to produce a hundred others who would praise the means through which they had regained their health and self-respect, even while asserting that their campaign of recovery had been a serious one. It is not germane to urge that other methods have their value. No one doubts this fact. And no one grudges these methods their successes and expansions, except insofar as it is true that the partial reforms instituted by them sometimes hold off more radical results, and do not so directly lead to the development in character that should go on hand in hand with improvement in health.

But these therapeutic systems, and all systems, including psychoanalysis, leave a large proportion of sufferers still uncured. Let each means of treatment, then, find its proper place; but let it be seen and acknowledged that psychoanalysis is the only method which can claim to put the patient back, in memory and insight, to the point, or series of points, in his development (in early childhood) at which he first grossly failed to respond adequately to the situation and the problem before him, and first learned, through a misuse of his imagination, his consciousness, and his will, the fatal art of cheating himself and leading (unwittingly) a double life. It is one of the remarkable signs of the far-reaching significance of the freedom with which we are endowed that we can use it to destroy our freedom; and a striking illustration of this is seen in the subtle, instinctive keenness with which the young child, when not sufficiently impelled by his own natural resources and not sufficiently aided by education, instead of taking each stage in his development as a stepping stone to the next, grows old indeed in years, but clings nevertheless, in secret, and without fully realizing the fact, to forms of thought and emotion which should have been outgrown and of which as a child he was secretly ashamed. Clear-sighted educators have long known the importance of this principle in the case of children somewhat older than those that I have now in mind. But it has remained for this group of investigators and those who have gradually affiliated themselves with them, to discover, point by point, the influences, first showing themselves at birth itself, and even pointing to a dim memory of

antenatal states and from then onward, which lead to the formation, in the hidden depths of the child's mind, of an emotional language (Autistisches Denken, Bleuler) and an emotional life, destined thereafter to play a large part in the determinations of his conduct. The emotions and excitements of this autistic life exist largely, not as transitions to something better and more permanent, but in and for themselves alone. They act to draw the desires away from the disinterested forms of love and life which constitute the natural goal of progress, and tend instead to the cultivation of egoistic forms of love, which may indeed have an object, but use that object as a mirror by means of which self-love may be intensified. No one who has not investigated the subject of the fantasy life of young—even the youngest—children in the manner and to the extent that it has now for the first time been shown to be possible to study it, can form any adequate idea of the contents of the young child's mind, contents which are destined to serve for the most part, fortunately, as the basis of wholesome forms of religion and art, but sometimes, instead of this, as the basis of morbid tendencies and morbid fears.

The evidence is very strong for the view that the appearance of the human mind among the evolutionary forces[1] introduces a new factor of enormous import. Even the infant and young child, by reason of the endowment of their mental structure have powers and obligations hitherto unrecognized. With their consciousness of themselves they acquire also the germs of consciousness of the scheme of the universe. They acquire the sense of power, responsibility, and personality, and also of weakness and dependence upon others and the subtle pleasure that goes with dependence. Like Phaeton, they are inclined to grasp the reins and drive the chariot of the sun, without having acquired the needful training or knowledge of the task before them. With their unbridled fancy they people the world and they utilize not only sticks and stones but everything, even (and very largely) their own sensations, as terms in which to express their passions and desires and longings.

[1] Attention has been called by Bergson and a host of others, to the significance of "life" (*pouseé vitale*, etc.) as a factor in evolution. The doctrine of which I now speak includes this but goes beyond it.

Then come reactions, loathings, self-depreciations, and forgetting in the form of repression which means really not forgetting but setting aside for further use. The child who is living externally a life of eminent self-satisfaction and propriety, may be indulging himself, almost without knowing it, in the aroma of pleasures and excitements which he had banished to the "unconscious" but to which he still keeps many secret avenues open.

As regards older children, Goethe says that his day dreams would have been very bad for him had he not learned to utilize them in his work and life. This is, of course, the prevention and the cure.

"The stream must be made to flow onward."

The great educator Dr. W. T. Harris[1] says: . . . "(for) it is evident that if the child is at any epoch of his long period of helplessness inured into any habit or fixed form of activity belonging to a lower stage of development, the tendency will be to arrest growth at that standpoint and make it difficult or next to impossible, to continue the growth of the child into higher and more civilized forms of soul activity."

It is the results of these arrests that the psychoanalytic method seeks to study and to modify. And if so much is said about sex issues in the process it is because the patients come very soon to realize that the strongest of their autistic "fixations," those which they are taught most to deprecate externally and learn to cherish internally, take the forms of sexual excitements. The sex tendencies in himself and in his (often largely selfish) passions for others who reflect himself are the most fascinating of the pleasures which he learns by repression to save for his indulgence. His tendency is then to "sexualize" many thoughts and feelings which were not primarily sexual. How can this be considered wholesome? How can a treatment through which the patient (and to some extent we all are patients) is enabled to see what is going on and to unmask the "confidence game" played by his lower nature on his higher nature, fail to commend itself as worthy of support? The method which attempts this should be judged with reference to its possibilities, and not its present achievements only. Its aim, in general

[1] Psychologic Foundations of Education, p. 142.

terms, is to help toward the solution of the external problems of human beings, by helping them, in *specific ways*, to solve their internal problems.

And this is a reasonable task. For the drama of the external world is played over, beforehand, in the minds and hearts of the virtual and actual personalities and organisms by which it is peopled. Let those who believe in the value of the method, but object to the way they think it used, test it out themselves. They owe it to their patients to attempt this.

THE PSYCHOPATHOLOGY OF A CASE OF PHOBIA: A CLINICAL STUDY

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The case of phobia of which this is a clinical study was one of church steeples and towers of any kind. The patient, a woman, about forty years of age, dreaded and tried in consequence to avoid the sight of one. When she passed by such a tower she was very strongly affected emotionally, experiencing always a feeling of terror or anguish accompanied by the usual marked physical symptoms. Sometimes even speaking of a tower would at once awaken this emotional complex which expressed itself outwardly in her face, as I myself observed on several occasions. Considering the frequency with which church and school-house towers are met with in every-day life, one can easily imagine the discomfort arising from such a phobia. Before the mystery was unravelled she was unable to give any explanation of the origin or meaning of this phobia, and could not connect it with any episode in her life or even state how far back in her life it had existed. Vaguely she thought it existed when she was about fifteen years of age and that it might have existed before that.

Now it should be noted that an idea of a tower with bells had in her mind no meaning whatsoever that explained the fear. It had no more meaning than it would have in anybody's mind. In the content of consciousness there was only the perception plus emotion and no corresponding meaning. Accordingly, I sought to discover the origin and meaning of the phobia by the so-called psycho-analytic method.

When I attempted to recover the associated memories by this

method, the mere mention of bells in a tower threw her into a panic in which anxiety, "thrills," and perspiration were prominent. Before making the analysis I had constructed a theory in my mind to the effect that a phobia for bells in a tower was a sexual symbolism, being led to this partly by the suggestiveness of the object and partly by the fact that I had found symbolisms of a sexual kind in her dreams.[1]

Analysis was conducted at great length and memories covering a wide field of experiences were elicited. When asked to think of bells in a tower, or each of these objects separately, there was at first a complete blocking of thought in that her mind became a blank. Later, memories which to a large extent, but not wholly, played in various relations around her mother (who is dead) as the central object came into the field of consciousness. Nothing, however, was awakened that gave the slightest meaning to the phobia even on the wildest interpretation. The patient, who had been frequently hypnotized by another physician, tended during the analysis to go into a condition of unusually deep abstraction, to such a degree that on breaking off the analysis she failed to remember, save very imperfectly the memories elicited. Such an abstraction is hypnosis.

Finally, after all endeavors to discover the genesis of the phobia by analysis were in vain, I tried another method. While she was in hypnosis I put a pencil in her hand with the object of obtaining the desired information through automatic writing. *While she was narrating some irrelevant memories of her mother,* the hand rapidly wrote as follows: "G.——— M.——— church and my father took my mother to Bi.——— where she died and we went to Br.——— and they cut my mother. I prayed and cried all the time that she would live and the church bells were always ringing and I hated them."

When she began to write the latter part of this script she became depressed, sad, indeed anguished; tears flowed down her cheeks and she seemed to be almost heartbroken. In other words, it

[1] In making the analysis, therefore, I was in no way antagonistic in my mind to the Freudian hypothesis.

appeared as if she were subconsciously living over again the period described in the script. I say subconsciously for she did not know what her hand had written or why she was anguished. During the writing of the first part of the script she was verbally describing other memories; during the latter part she ceased speaking.

After awakening from hypnosis and when she had become composed in her mind she narrated at my request the events referred to in the script. She remembered them clearly as they happened when she was about fifteen years of age. It appeared that she was staying at that time in G.——— M.———, a town in England. Her mother, who was seriously ill, was taken to a great surgeon to be operated upon. She herself suffered great anxiety and anguish lest her mother should not recover. She went twice a day to the church to pray for her mother's recovery and in her anguish declared that if her mother did not recover she would no longer believe in God. The chimes in the tower of the church, which was close to her hotel, sounded every quarter hour; they got on her nerves; she hated them; she could not bear to hear them, and while she was praying they added to her anguish. Ever since that time the ringing of bells had continued to cause a feeling of anguish. This narrative was not accompanied by emotion as was the automatic script.

It now transpired that it was the *ringing* of the church bells, or the *anticipated ringing* of bells, that caused the fear, and not the perception of a tower itself. When she saw a tower she feared lest bells should ring. This was the object of the phobia.[1] She could not explain why she had never before connected her phobia

[1] I want to emphasize this point, because certain students assuming the well-known alleged sexual symbolism as the meaning of steeples and towers will read and have read such an interpretation into this phobia. As a matter of fact, although these objects had been originally alleged by the subject herself to be the objects of the fear it was done thoughtlessly as the result of careless introspection. Later she clearly distinguished the true object. The alleged steeples and towers were no more the object than the churches and school-houses themselves. They bore an incidental association only, and only indicated where the ringing of bells might be expected to be heard having been an element in the original episode. Nor were bells qua bells the object of the phobia, but the ringing of bells of the kind that recalled the mother's death. In other words, the fear was of bells with a particular meaning. Nor was the fear absolutely limited to tower-bells, for it transpired that the subject had refrained from having, as she desired, an alarm bell arranged in her house in the country (in case of fire, etc.) because of her phobia.

with the episode she described. This failure of association as we know is not uncommon, and in this case was apparently related to a determination to put out of mind an unbearable episode associated with so much anguish. There had been for years a more or less constant mental conflict with her phobia. The subject had striven not to think of or look at belfries, churches, school-houses, or any towers, or to hear the ringing of their bells, or to talk about them. She had endeavored to protect herself by keeping such ideas out of her mind. Before further analyzing the case there are two points which are well worth calling attention to:

1. When the subject subconsciously described the original childhood experience by automatic script there was intense emotion—fear—which emerged into consciousness without her knowing the reason thereof. When, on the other hand, she later from her conscious memories described the same experience there was no such emotion. In other words, it was only when the conserved residua of the experience functioned co-consciously and autonomously as a dissociated, independent process that emotion was manifested. So long as the memories were described from the view-point of the matured adult personal consciousness there was no emotion. As a subconscious process they were unmodified by this latter view-point. This suggests at least that when the phobia was excited by the sight of the idea of a tower it was due likewise to a subconscious process and that this was one and the same as that which induced the experimental phobia.

2. The phraseology of the script is noticeable. The account is just such as a child might have written. It reads as if the conserved thoughts of a child had awakened and functioned subconsciously.

From this history, so far as given, it is plain that the psychosis in one sense is a recurring antecedent experience or memory, but it is only a partial memory. The whole of the experience does not recur but only the emotion in association with the ringing of bells. The rest of that experience, viz., the idea of the possible death of her mother with its attendant grief and anguish associated with the visits to the church, the praying for recovery, and finally the

realization of the fatal ending, all that which originally excited the fear and *gave the ringing-of-bells-in-a-tower meaning* was conserved as a setting in the unconscious. That this rest of the experience was conserved was shown by the fact that it could be recalled not only by automatic writing but to conscious memory, although not through association with the phobia. From this point of view the fear of bells ringing may be regarded as a recurrence of the original fear—that of her mother's death—now derived from a subconsciously functioning setting. The child was afraid to face her grief and so now the matured adult was also afraid.

From another point of view the ringing of bells may be regarded as standing for, or a symbol of, her mother's death with which it was so intimately associated, and this symbol awakened the same fear as did originally the idea itself of the death. An object may still be a symbol of another, although the association between the two cannot be recalled. (The transference of the emotional factor of an experience to some element in it is a common occurrence, *e. g.*, a fear of knives in a person who has had the fear of committing suicide.)

The discovered antecedent experiences of childhood then give a hitherto unsuspected meaning to the ringing of bells. It is *a* meaning—the *mise en scène* of a tragedy of grief and a symbol of that tragedy. But was that tragedy with its grief the *real* meaning of the child's fear, or, perhaps more correctly, the *whole* of the meaning? And is it still the meaning in the mind of the adult woman? Does the mere conservation of a painful memory of grief explain its permanent recurrent subconscious functioning during twenty-five years, well into adult life, so that the child's emotion shall be reawakened whenever one element (bell-tower) of the original experience is presented to consciousness? And still more, can the persistence of a mere association of the affect with the object independently of a subconscious process explain the psychosis? Either of these two last propositions is absured on its face as being opposed to the experience of the great mass of mankind. The vast majority of people have undergone disturbing, sorrowful, or fear-inspiring experiences at some time during the

course of their lives and they do not find that they cannot for years afterward face some object or idea belonging to that experience without being overwhelmed with the same emotion. This emotion in the course of time subsides and dies out. A few, relatively speaking, do so suffer and then, because contrary to general experience, it is called a psychosis.

We must then seek some other and adequate factor in the case under examination. When describing the episode in the church, the subject stated that on one occasion she omitted to go to church to pray and the thought came to her that if her mother died it would be due to this omission, and it *would be her fault.* The "eye of God,"[1] she thought, was literally upon her in her every daily act, and when her mother did die she thought that it was God's punishment of herself because of that one failure. Consequently she thought that *she was to blame for her mother's death—that her mother's death was her fault.* She feared to face her mother's death, not because of grief—that was a mere subterfuge, a self-deception—but because she thought she was to blame; and she feared to face towers with bells, or rather the ringing of bells, because they symbolized or stood for that death (just as a tombstone would stand for it), and in facing that fact she had to face her own fancied guilt and self-reproach, and this she dared not do. This was the real fear, the fear of facing her own guilt. The emotion then was not only a recurrence of the affect associated with the church episode but a *reaction to self-reproach.* The ringing of bells, somewhat metaphorically speaking, reproached her as Banquo's ghost reproached Macbeth.

All this was the child's point of view. But I found that the

[1] This idea had its origin in a child's fairy tale and had been fostered by the governess as a useful expedient in enforcing good behavior. The child accepting the fairy legend believed the Eye of God was always on her and everyone in the world and observed all that each did or omitted to do. The legend excited her imagination and she used to think about it and wonder how God could keep His eye on so many people as there were in the world. At a still earlier age, when she was about eight, she had thought her little brother's death was also her fault because she had neglected one night, at the time of his illness, God's eye being upon her, to say her prayers. For a long time afterward she suffered similarly from self-reproach. It is interesting to compare the outgrowing with maturity of this self-reproach with the persistence of the later one, evidently owing to the reasons given in the text.

patient, an adult woman, *still believed and obstinately maintained* that her mother's death was her fault. She had never ceased to believed it. Why was this? Why had not the unsophisticated belief of a child become modified by the maturity of years? It did not seem to be probable that the given child's reason was the real adult reason for self-reproach. I did not believe it. A woman forty years of age could not reproach herself on such grounds. And even if this belief had been originally the real reason, as a matter of fact she had outgrown the child's religious belief. She was a thoroughgoing agnostic. Further probing brought out the following:

Two years before her mother's death, the patient, then aged thirteen years, owing to her own carelessness and disobedience to her mother's instructions, had contracted a "cold," which had been diagnosticated as incipient phthisis. By the physician's advice her mother took her to Europe for a "cure," and was detained there (as she believed) for two years all on account of the child's health. At the end of this period a serious, chronic disease from which the mother had long suffered, was found to have so developed as to require an emergency operation. The patient still believed and argued that if her mother had not been compelled to take her abroad she (the mother) would have been under medical supervision at home, would have been operated upon long before, and in all probability would not have died. Furthermore, as the patient had heedlessly and disobediently exposed herself to severe cold and thereby contracted the disease, compelling the sojourn in Europe, she was to blame for the train of circumstances ending fatally.

All this was perfectly logical and true, assuming the facts as presented. Here then was the real reason for the patient's persistent belief that her mother's death was her fault and the persistent self-reproach. *It also transpired that all this had weighed upon the child's mind and that the child had likewise believed it.* So the child had two reasons for self-reproach: One was neglecting to pray and the other was being the indirect cause of the fatal operation. Both were intensely believed in. The first, based on the "eye of God" theory, she had outgrown but the other had persisted.

Summing up our study to this point. All these memories in-

volving grief, suffering, self-reproach, bells, and mother formed an unconscious setting which gave meaning to bells in towers and took part in the functioning to form a psychic whole. The conscious psychosis was first the emergence into consciousness of two elements only, the perception and the affect; and the fear was a reaction to self-reproach, a fear to face self blame.

Now, even if the mother's death were logically, by a train of fortuitous circumstances, the patient's fault, why did an otherwise intelligent woman lay so much stress upon an irresponsible child's behavior? The child after all behaved no differently from other children. People do not consciously blame themselves in after life for the ultimate consequences of childhood's heedlessness.

According to common experience such self-reproaches do not last into adult life without some continuously acting factor.

A search in this case into the unconscious brought to light a persisting idea that when events in her life happened unfortunately it was due to her fault. It had cropped out again and again in connection with inconsequential as well as consequential matters. She had, for instance, been really unable on many occasions to leave home on pleasure trips for fear lest some accident might happen within the home and consequently it would be due to her fault; and if away she was in constant dread of something happening for which she would be to blame. It was not a fear of what might happen—an accident to the children, for example—but that it would be her fault. I have heard her, when some matter of apparently little concern had gone wrong, suddenly exclaim, "Was it my fault?" her voice and features manifesting a degree of emotion almost amounting to terrror. When her brother died (still earlier, before her mother's death) she had blamed herself for that death, as later with her mother, on the same religious grounds. This self-reproach for happenings, fancied as due to her fault, has frequently appeared in her dreams. It would take us too far afield to trace the origin and psychogenesis of this idea. Suffice to say, it can be followed back to early childhood when she was five or six years of age. She was a lonely, unhappy child. She thought herself ugly and unattractive and disliked, and that so it always would be through life, and it was all her fault because she was ugly, as she

thought.[1] The instinct of self-abasement (McDougall)[2] or negative self-feeling (Ribot) dominated the personality as the most insistent instinct and from its intensity within the self-regarding sentiment (McDougall), formed a sentiment of self-depreciation. She wanted to be liked and believed it to be her own fault that, as she fancied, she was not, and reproached herself accordingly. This sentiment of self-depreciation with its impulse to self-reproach has persisted, as with many people, all her life and has been fostered by unwise and thoughtless domestic criticism. The persistence to the present day of this impulse to self-reproach is shown in the following observation: Quite recently this subject began to suffer from general fatigue, insomnia, distressing dreams, hysterical

[1] Another example of this idea and of the way it induced a psychosis is the following: She had an intense dislike to hearing the sound of running water. This sound induced an intense feeling of *unhappiness and loneliness*. This feeling was so intense that whenever she heard the sound of running water she endeavored to get away from it. The sound of a fountain or rain water running from a roof, for example, would cause such unpleasant feelings that she would change her sleeping room to avoid them. Likewise drawing water to fill the bath-tub was so unpleasant that she would insist upon the door being closed to exclude the sound. She could give no explanation of this psychosis. It was discovered in the following way. She had been desirous of finding out the cause and we had discussed the subject. I had promised that I would unravel the matter in due time, after the other phobia had been cured. I then hypnotized her and while she was in hypnosis and just after we had completed the other problem, she remarked that a memory of the running water association was on the verge of emerging into her mind. She could not get it for some time and then, after some effort, it suddenly emerged. She described it as follows: "It was at Bar Harbor. I was about eight years of age. There was a brook there called Duck Brook. The older girls used to go up there on Sundays for a walk with the boys. I went with them one Sunday accompanied by the governess and was standing by the brook with a boy. It was a very noisy brook, the water running down from the hillside. While I was standing by the brook watching the running water the boy left me to join the other girls who had gone off. I thought that was the way it would always be in life; that I was ugly and that they would never stay with me. I felt lonely and unhappy. During that summer I would not join parties of the same kind, fearing or feeling that the same thing would happen. I stayed at home by myself and when I refused to go it was attributed to sullenness. They did not know my real reasons. Ever since I have been unable to bear the sound of running water which produces the feeling of unhappiness and loneliness, the same feeling that I had at that time. I thought then that it was all my fault because I was ugly." It was then tentatively pointed out at some length to the subject that as she now knew all the facts which had been brought to the "full light of day," etc., she of course would no longer have her former unpleasant emotions from the sound of running water. Hereupon to put the question to the test, I reached out my hand and poured some water from a caraffe, by chance standing by, into a tumbler, letting the water fall from a height to make a sound. At once she manifested discomfort and sought to restrain me with her hand. The setting had to be changed. This was easily done by leading her to see that her childhood's ideas had been proved by life's experiences to be false. When this became apparent she laughed at herself, and the psychosis ceased at once.

[2] Social Psychology.

crying, indefinable anxiety, and sort of twilight states or extreme states of abstraction. In these states she became oblivious of her environment, did not hear the conversation going on about her, nor answer when directly spoken to. This became so noticeable that she became the jest of her companions. In these states her mind was always occupied with reveries, though mostly pleasant, regarding a very near relative who had died about six months previously. Her dreams also concerned this relative. It appeared therefore probable on the face of the symptoms that they were in some way related to this relative's death.

Now it transpired, as I already knew, that the relative had died under somewhat tragic circumstances and that our subject's experience during the last illness was unusually distressing and sorrowful. *This experience, she asserted, she could not bear to speak or even think about, and over and over again had refused to do so, and put it out of her mind. She further asserted that her reason for this attitude was the distressing nature of the scenes in which she took part.*

Now I did not believe that this was the true reason, although given in good faith. It was improbable on its face. To say that a grown woman, forty years of age, could not do what every woman can do, tolerate sorrowful memories, simply because they were sorrowful, and must perforce put them out of mind, is sheer nonsense. There must be some other reason.

On examining a dream it was found to be peculiar in one respect. It was not an imaginative or fantastic composition, but a detailed and precise living over again of the scenes at the death bed; that is to say, it was a sort of somnambulistic state. In recalling this dream[1] she could not for some time recover the ending. Finally it "broke through," as she expressed it. The dream was as follows: First came many details of the vigil of the last night of the illness; then she returned to her room and to bed to snatch a few moments sleep; she was awakened by the husband of the dying relative appearing in her room. He sat on the edge of her bed and said to her, "All is over." Up to this point the facts of the dream were

[1] This was done in hypnosis, the dream being forgotten when awake.

actual representations in great detail of the actual facts as they had occurred, but at this moment the dream presented a fact which had not occurred in the real scene; she suddenly, in the dream, sat up in bed and exclaimed, "My God! then I ought to have sent for the doctor!"

Here was the key to the intolerance for memories of the illness of the relative and the death bed scene. What had happened was this: The question had arisen early in the illness whether or not a doctor should be sent for from London in consultation. The expense, owing to the distance, would have been considerable. The whole responsibility and decision rested upon the subject. Against the opinion of other relatives she had decided that it was inadvisable. After the fatal ending the question had arisen again whether or not she ought to have sent for the consultant, and she had been tormented by the doubt as to whether she did right; *was the fatal result her fault?* Although she had reasoned with herself that her decision was good judgment and right, still there had always lurked a doubt in her mind. She was also somewhat disturbed by the thought of what the husband's opinion might be.

The real reason why she could not tolerate the memories of the last illness of this relative, and the psychogenesis of the symptoms now was plain; it was not grief but self-reproach with its instinct of self-abasement. The memories brought to her mind that the fault was hers and with the thought came self-reproach. *This self-reproach she was afraid of and unwilling to face.*

Now follows the therapeutic sequel. The relative's illness at the beginning was in no way of a dangerous nature and the proposed consultation had nothing to do with the question of danger to life. The death was due to purely an accidental factor and could not have been foreseen. When I assured her in hypnosis, *with full explanation*, that her decision had been medically sound, as it was, the change in her mental attitude was delightful to look upon. "Wasn't it my fault! Wasn't it my fault," she exclaimed in excitement. Anxiety, dread, and depression gave way to exhilaration and joyousness. Thereupon she woke up completely relieved in mind, and retained the same feeling of joy, but without knowing the

reason thereof. The explanation was repeated to her in the waking state and she then fully realized (as she did also in hypnosis) that her previous view was a pure subterfuge and fully appreciated the truth of the discovered reason for her inability to face her painful memories. The twilight states, the insomnia and the distressing dreams, the anxiety, and other symptoms ceased at once.

Returning to the phobia for bells, in the light of all these facts, the patient's belief that her mother's death was her fault and the consequent self-reproach were obviously only a particular concrete example of a lifelong emotional tendency originating in the experiences of childhood to blame herself; and this tendency was the striving to express itself of the instinct of self-abasement (with the emotion of self-subjection) which, incorporated within "the self-regarding sentiment" (McDougall), was so intensely cultivated and had played so large a part in her life. Indeed, this instinct had almost dominated her self-regarding sentiment and had given rise time and again to self-reproach for accidental happenings. It now specifically determined her attitude of mind toward the series of events which led up to the fatal climax and determined her judgment of self-condemnation and self-reproach. These last most probably received increased emotional force from the large number of roots in painful associations of antecedent experiences (particularly of childhood) in which the self-regarding sentiment, self-debasement, and self-reproaches were incorporated.[1] *Nevertheless the fear was of a particular concrete self-reproach.* The general tendency was of practical consequence only so far as it explained the particular point of view and might induce other self-reproaches.

As a general summary of this study it would appear that we can postulate a larger setting to the phobia than the grief-inspiring

[1] For instance, when I came to the therapeutics I found in abstraction that the patient did not want to give up her point of view "because," as she said, "it forms an excuse so that when I feel lonely, if there is nothing else to be lonely about, I have that memory and point of view to fall back upon as something to justify my crying and feeling lonely and blue."

When she now feels blue and cries, as happens occasionally and she asks herself Why? she drifts back in her mind to childhood and remembers she was lonely, and then cries the harder. Then she vaguely thinks of her mother's death being her fault. She likes, therefore, to hold on to this as a peg on which to hang any present feeling of blueness and loneliness.

experiences attending her mother's death. The unconscious[1] complex included the belief that she was to blame and the sentiment of self-reproach, and the whole gave a fuller meaning to the ringing of bells in a tower. The fear besides being a recurring association was also a reaction to the subconsciously excited setting of a fancied truth or self-accusation. Although excited by towers and steeples the fear was really of self-reproach. Towers, steeples, and bells not only in a sense symbolized her mother's death but her own fancied fault. It was in this sense and for this reason that she dared not face such objects. The conscious and the unconscious formed a psychic whole.[2]

Now in reaching these conclusions see how far we have travelled: Starting with an alleged phobia for towers, we find it is more correctly one of ringing of bells, but without conscious association; then we reach a childhood's tragedy, then a self-reproach on religious grounds, then a belief in a fault of childhood behavior culminating in a life-long self-reproach—the causal factor and psychologically the true object of the phobia; and between this last self-reproach and the phobia no conscious association.

The *therapeutic* procedure and results are instructive. As the fear was induced by a belief in a fancied fault exciting a self-reproach, obviously if this belief should be destroyed the self-reproach must cease and the fear must disappear. And when all the facts were brought to light, the patient, as is usual, recognized the truth of them. She also recognized fully and completely the real nature of the fear, of the self-blame and of the self-reproach.

[1] I distinguish between unconscious and subconscious in that the former (according to my terminology) is a subdivision of the latter and relates only to the conserved residua of past experiences and processes which have no psychological equivalent, while subconscious also includes, besides these, conscious processes.

[2] Some I have no doubt will insist upon seeing in towers with bells a sexual symbol, and in the self-reproach a reaction to a repressed infantile or other sexual wish. But I cannot accede to this view: (1) Because a tower was not only not the real object of the phobia but not even the ostensible object which was the ringing of bells; (2) because it is an unnecessary postulate unsupported by evidence, and (3) because, in fact, the associative memories of early life were conspicuously free from sex knowledge, wishes, curiosity, episodes, and imaginings, nor was there any evidence of the so-called "mother complex," or "father complex," or any other sexual complex that I could find after a most exhaustive probing. The impulses of instincts other than sexual are sufficient to induce psychical trauma, insistent ideas, and emotion. To hold otherwise is to substitute dogma for the evidence of experience.

There remained no lingering doubt in her mind; nevertheless, the bringing to "the full light of day" of all this did not cure the phobia. As the first procedure in the therapeusis it was pointed out that it was contrary to common sense to blame herself for the heedlessness of a child; that all children were disobedient; that she would have been a little prig if she had been the sort of a child that never disobeyed, and that she would not have blamed any other child who had behaved in a similar way under similar circumstances, and so on. She simply said that she recognized all this intellectually as true and yet, although it was the point of view which she would take with another person in the same situation, it did not in any way alter her attitude toward herself. In other words, the bringing to the full light of day of the facts did not cure the phobia. It was necessary to change the setting of her belief. *To do this either the alleged facts had to be shown to be not true or else new facts had to be introduced which would give them a new meaning.* This, briefly told, was done in the following way:

She was put into light hypnosis in order that exact and detailed memories of her childhood might be brought out. Then, through her own memories, it was demonstrated, that is to say, *the patient herself demonstrated,* that there was considerable doubt about her having had phthisis at all, that she was not taken to the usual places of "cures" for phthisis but sojourned in the gay and pleasant cities and watering places of Europe; that her mother really stayed in Europe because she enjoyed it and made an excuse of her daughter's health not to come home; that she might have returned at any time but did not want to do so; and that the fault lay, if anywhere, with her physician at home. When this was brought out the patient remarked, "Why, of course, I see it now! My mother did not stay in Europe on account of my health but because she enjoyed it, and might have returned if she had wanted to. I never thought of that before! It was not my fault at all!" After coming out of hypnosis the facts as elicited were laid before the patient; she again said that she saw it all clearly, as she had done in hypnosis, and her whole point of view was changed.

The therapeutics, then, consisted in showing that the alleged

facts upon which the patient's logical conclusions had been based were false. The setting thereby was altered, and a new and true meaning given to the real facts. The result was towers and steeples no longer excited fears, the phobia ceased at once—an immediate cure.[1]

[1] It is worth noting that between the bringing to the "full light of day" the facts furnished by the analysis and the cure a full year and a half elapsed during which the phobia continued. The "cure" was effected at one setting. The original study was undertaken on purely psychological grounds; the cure for the purpose of completing the study.

DISTURBANCES OF THE HEART-BEAT IN THE DOG CAUSED BY SERUM ANAPHYLAXIS[1]

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INTRODUCTION

The present investigation is a continuation of our electrocardiographic study of the cardiac disturbances caused by serum anaphylaxis, which was begun in the rabbit.[2] The literature concerning the effect of anaphylaxis on the heart of the dog is not extensive, and is entirely opposed to the idea that the dog's heart is primarily affected by anaphylaxis. Biedl and Kraus[3] exclude on theoretical grounds any cardiac effect during the anaphylactic reaction in dogs. Eisenbrey and Pearce[4] examined the heart of anaphylactic dogs with a myocardiograph, but failed to detect any primary effect on the heart muscle. The ordinary tracings with the myocardiograph, however, are too condensed to permit the detection of partial heart-block, and the finer degrees of an abnormal contraction are not revealed at all.

The electrocardiographic method proved so satisfactory when working with rabbits, revealing cardiac disturbances which could

[1] A preliminary note appeared in the Centralbl. f. Physiol., 1913, xxvii, 383.
[2] A preliminary note was published in the Centralbl. f. Physiol., 1913, xxvii, 1. A full report, Jour. Exper. Med., 1913, xviii, 450.
[3] See their latest statement, Kraus-Levaditi's Handbuch Ergänzbd., i, 258.
[4] Jour. Pharmacol. and Exper. Therap., 1912, iv, 27.

not be recorded by the ordinary graphic method, that it seemed advisable to apply this method to the study of the cardiac activity of the dog in anaphylaxis. Findings in another series of experiments on dogs, performed by one of us (Auer)indicated that cardiac disturbances would probably be revealed by electrocardiograms, for a certain number of dogs died acutely within twenty to forty minutes after the injection of the second dose of horse serum, and immediate autopsy showed that the heart had largely lost its irritability and contractility when stimulated mechanically or electrically. As these changes were similar to those observed in the rabbit[1] and as the latter showed undoubted disturbances in the heart's activity when observed directly[2] or by the electrocardiograph, it seemed reasonable to expect some cardiac disturbances also in the dog.

Most investigators, in speaking of the anaphylactic reaction, use the term "anaphylactic shock." Now the term "shock," though by no means a well-defined physiological entity, yet means either a low blood-pressure (vascular shock) or a rapid, feeble pulse (cardiac shock) or a combination of the two.[3] The term "shock," therefore, may be applied to the anaphylactic reaction of the dog and the rabbit, but not to that of the guinea-pig, for the latter animal dies of an asphyxia.[4]

EXPERIMENTS

The dogs used varied in weight from 6 to 14 kilos. Sensitization was produced by the subcutaneous injection of 10 c.c. of horse serum, 5 c.c. in each flank. The period of incubation lasted from twenty-two to sixty-two days. The degree of sensitization obtained varied considerably, as far as cardiac effects are concerned, though all showed the characteristic drop in blood-pressure.[5] No definite

[1] Auer, Jour. Exper. Med., 1911, xiv, 494. [2] Loc. cit., p. 483.
[3] See Howell, Vaughan's Festschrift, 1903, p. 51. George Wahr, Ann Arbor, publisher.
[4] Auer and Lewis, Jour. Exper. Med., 1910, ii, 172.
[5] The blood-pressure was not recorded in the first two experiments. Both of these dogs recovered completely and were used again after some weeks.

relation could be detected between the length of sensitization and the toxic effect of reinjection; outspoken cardiac effects, for example, were obtained in one set after sixty-one, thirty-five, thirty-seven, and forty days, while other dogs after practically the same intervals showed no disturbances of the heart-beat.

The experiments were performed as follows: After etherization narcosis was kept up by means of intratracheal insufflation. Cannulas were then introduced into a carotid artery and an external jugular vein. The carotid blood-pressure was read by means of a mercury manometer, the connecting tubing being filled with a half saturated solution of sodium sulphate. The toxic dose of horse serum, usually 20 c.c., was always injected into a jugular vein. In eight experiments this injection was repeated after the animal had partly recovered from the effects of the first one. It may be added that the horse serum employed was about nine months old. The injections required about one minute. In four experiments the vagi were cut in the neck before the toxic injection of horse serum was given.

The cardiac activity was recorded by means of the electrocardiograph, the Edelmann large model being used. The string of the galvanometer was always so adjusted that the passage of one millivolt gave a movement of one centimeter on the curves. The electrodes were always applied to the right foreleg and left hindleg. In most experiments, non-polarizable electrodes, attached to the animal by gauze in salt solution, were used. In others gold-plated needles, brazed on curved, lacquered brass plates provided with a binding post, were inserted under the skin; the plates, from which the wires led to the galvanometer, were held in position by tapes. Both methods gave identical results. Control curves were usually made before and after the operation and, in the early experiments, also before and after the manometer recorded the blood-pressure. Electrocardiograms were then taken before and after the injection and at frequent intervals subsequently, usually every fifteen seconds for several minutes—then at less frequent intervals until all apparent effects had disappeared. The movements of the string were always carefully watched and curves taken whenever any change was noted. The time consumed by one experiment varied between

ten minutes and two hours. Only one animal, XII, succumbed acutely during the experiments; dogs VIII, IX, X, and XVI survived for one or two days and then died. The other dogs were usually killed at the end of the experiment by injecting strophanthin intravenously. At the end of this paper a specimen protocol is appended. All experiments were carried out in this manner.

The most striking effect of the anaphylactic reaction was the well-known marked fall in blood-pressure, first described by Biedl and Kraus.[1] This occurred immediately after injection in the ten experiments in which the blood-pressure was observed. The average fall was 106 mm. Hg. The pressures before the injections averaged 126 mm. Hg., and the lowest pressures observed after the injections averaged 19.5 mm. Hg. The time required for this fall of blood-pressure averaged about three and one-half minutes, but varied in the different experiments from one-half to seven minutes. Six of the experiments showed practically no changes in the heart-beat, except changes in rate. There was no evidence of disturbance of conduction from auricles to ventricles, and the electrocardiograms showed no abnormalities in form. In six other experiments, however, definite alterations were observed in the electrocardiograms, in addition to changes in rate, which were evidently part of the anaphylactic reaction.

The dogs, in which a *change of rate* was the only disturbance of cardiac activity, showed almost constantly a gradual reduction of the cardiac rate throughout the experiment, and in only one instance was the rate higher after the injection than before. Thus in experiment VII, during a drop in the blood-pressure from 140 to 30 mm. Hg., the heart-rate gradually fell from 210 to 140 beats per minute, and continued at this rate until the end of the experiment, although the blood-pressure rose later to 85 mm. Hg. In three other experiments, in one of which the vagi were cut, similar results were observed, while in the two remaining experiments, changes in rate were very slight. The six experiments with definite cardiac disturbances showed a less constant change in rate. In two, a gradual fall in rate took place, while in two there was but little change.

[1] Wiener klin. Woch ,1909, xxii, 365. See also Arthus Arch. Internat. de Physiol., 1910, ix, 179.

In one of the remaining two experiments (No. VIII, see Chart I) the rate fell somewhat, but rose again with the rise of blood-pressure,

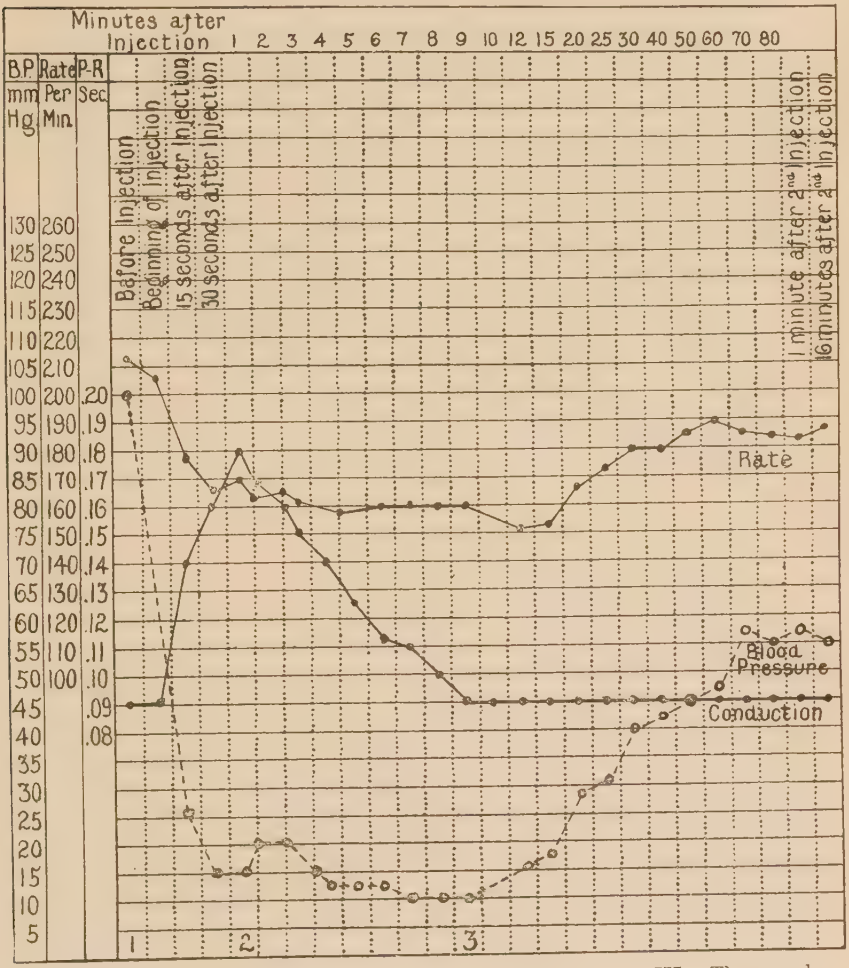

CHART I.—Curve constructed from the records of Experiment VIII. The records in Figs. 1, 2, and 3 were obtained at the time in the experiment marked by 1, 2, and 3 at the bottom of the curve. The relation of changes in rate, blood-pressure, and conduction, and the time of injection of the horse serum is shown. Upper solid line = cardiac rate per minute. Lower solid line = conduction (P-R) time in seconds. Broken line = blood-pressure in mm. of mercury.

while in the other the rate fluctuated considerably in spite of a sudden fall and continued relatively low blood-pressure. In this

experiment the rate rose from 175 beats per minute before the injection to 260 beats thirty seconds after the injection. In three minutes more it fell again to 150, but rose again to 212 beats three minutes later. This was the only experiment in which a sharp rise in cardiac rate accompanied the marked fall in blood-pressure, but even here the increased rate was of short duration and seems to have been independent of the fall in blood-pressure. It may, therefore, be stated, in general, that the changes in cardiac rate were not marked, and usually consisted of a gradual decrease which seemed quite independent of changes in blood-pressure.

Definite *disturbances in cardiac activity* were seen in six experiments. These disturbances were indicated in the electrocardiograms by abnormal relations of waves of auricular and ventricular activity and by significant changes in the form of the ventricular portions. In five experiments there was a delay in the conduction of impulses from auricles to ventricles which resulted in the prolongation of the P–R time to more than 0.12 second. In two of these experiments the disturbance of conduction was so marked that partial auriculoventricular block occurred. Definite changes in form occurred in the ventricular portions of the electrocardiograms of three experiments. These changes and the disturbances in conduction occurred both in dogs with intact vagi and in others where they had been cut.

A temporary lengthening of the conduction (P–R) time occurred in two experiments (Nos. VIII and XV). In experiment VIII the vagi were intact. Before the injection the blood-pressure was 100 mm. Hg., the rate 212 per minute and the conduction (P R) time 0.09 second. The form of the electrocardiogram was that of a normal sequential beat (Fig. 1). One minute after the injection of 20 c.c. of horse serum, the blood-pressure had fallen to 15 mm. Hg., the conduction (P–R) time was lengthened to 0.18 second and the rate was slowed to 175 beats per minute (Fig. 2). During the next fourteen minutes, the blood-pressure and cardiac rate showed no definite variation, but the conduction time gradually shortened and had returned five minutes before any rise of blood-pressure occurred to 0.09 second (Fig. 3). The conduction time showed no further change during the two hours in which curves

were made. The relation of the changes in rate, in conduction and in blood-pressure is seen in the accompanying curve (Chart I).

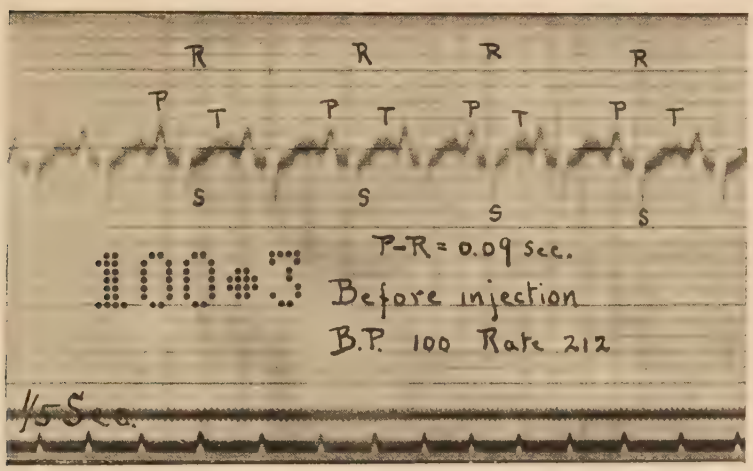

FIG. 1.—Experiment VIII. Vagi intact. Electrocardiogram before injection. Conduction (P–R) time = 0.09 second. Blood-pressure = 100 mm. Hg. Rate = 212. (Time in one-fifth and one-fiftieth seconds.)

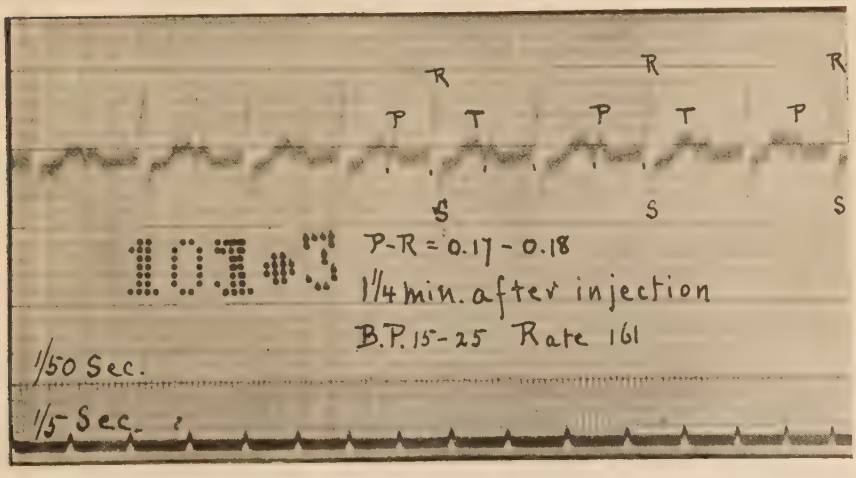

FIG. 2.—Experiment VIII. One and a quarter minutes after injection. Conduction (P–R) time = 0.17 to 0.18 second. Blood-pressure = 15 to 25 mm. Hg. Rate = 161. Shows the delay in conduction.

In experiment XV both vagi were cut. The injection of 20 c.c. of horse serum was followed here also by a definite prolongation of the conduction time from 0.1 second (Fig. 4) to 0.14 second

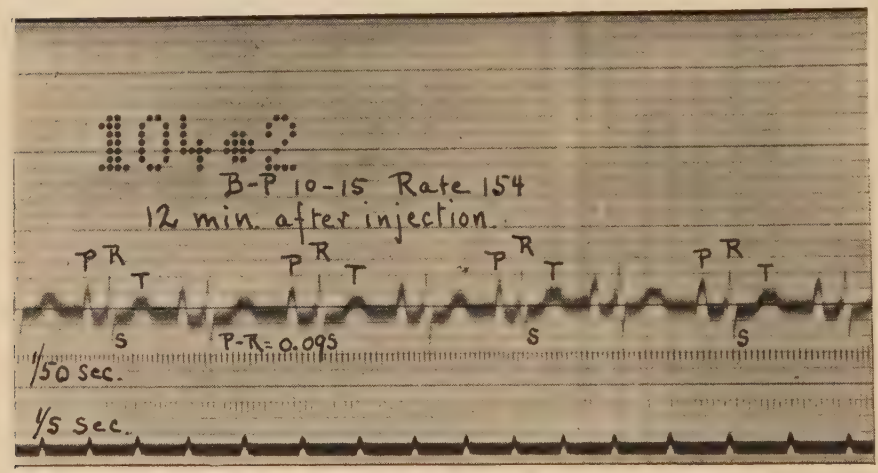

FIG. 3.—Experiment VIII. Twelve minutes after injection. Conduction (P–R) time = 0.09 second. Blood-pressure = 10 to 15 mm. Hg. Rate = 154. Shows the return to normal conduction without any increase in blood-pressure.

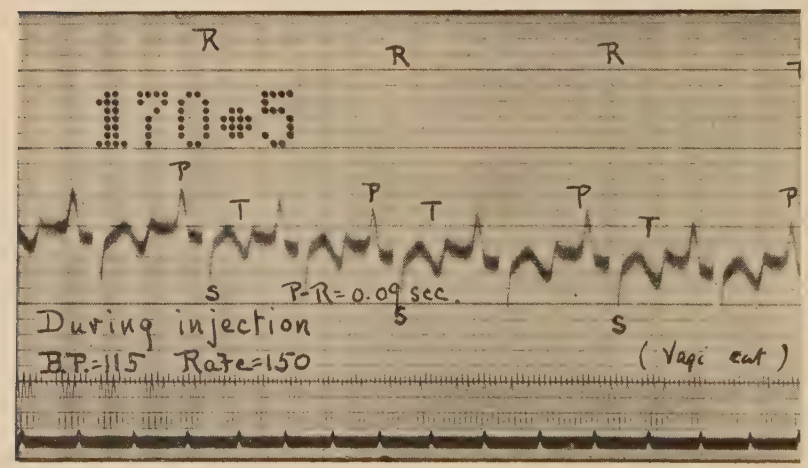

FIG. 4.—Experiment XV. Vagi cut. Electrocardiogram during injection. Conduction time = 0.09 second. Blood-pressure = 115 mm. Hg. Rate = 150.

(Fig. 5), which continued for thirteen minutes and then returned to normal. The blood-pressure fell from 115 mm. Hg. to 32 mm. Hg. and did not rise beyond 40 mm. Hg. for thirty-six minutes.

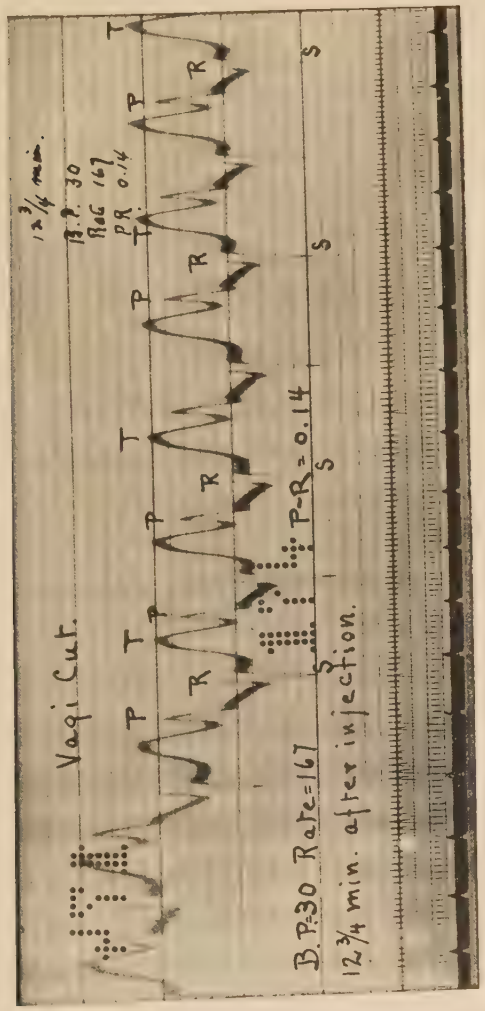

Fig. 5.—Experiment XV. Twelve and three-quarter minutes after injection. Conduction time = 0.14 second. Blood-pressure = 30 mm. Hg. Rate = 167. Shows marked changes in the form of the ventricular complexes and delay in conduction.

There was almost no change in rate throughout the experiment. The most striking feature in this experiment, however, is the gradual change in the form of the ventricular complexes. This change began

about one minute after the injection. The R-waves became smaller, the S-waves became more prominent, and the T-waves, which were

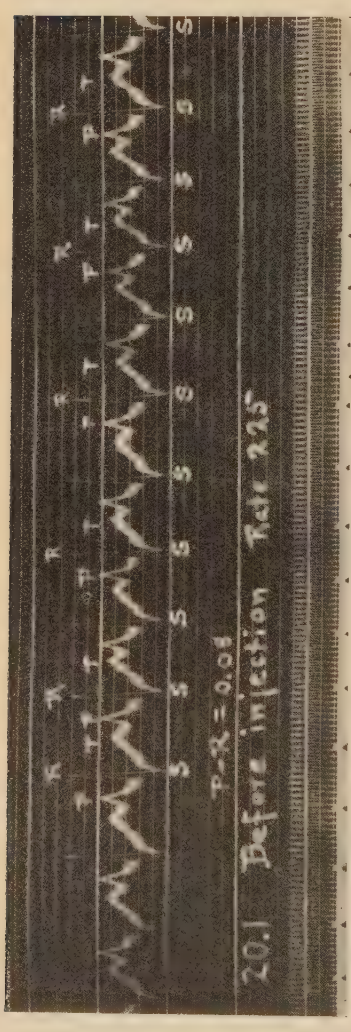

FIG. 6.—Experiment I. Vagi intact. Electrocardiogram before injection. Conduction time = 0.08 second. Rate = 225.

FIG. 7.—Experiment I. Three minutes after injection. Onset of partial auriculoventricular dissociation. Auricular rate = 267. One auricular beat in every eight is blocked. Conduction time varies from 0.12 to 0.28 second.

inverted or negative at first, disappeared and then increased gradually in size. The change was most marked twelve and three-quarter minutes after the injection (Figs. 4 and 5), when the

complexes began to revert gradually to the normal, so that twenty-seven minutes after the injection the electrocardiogram resembled that obtained before the injection. Experiment XVI, in which the vagi were intact, showed changes very similar to those seen in

FIG. 8.—Experiment I. Nine minutes after injection. Partial auriculoventricular dissociation. Auricular rate = 233. One auricular beat in every four is blocked. Conduction time varies from 0.14 to 0.26 second. A change in form of the ventricular complexes similar to that in Experiment XV is seen.

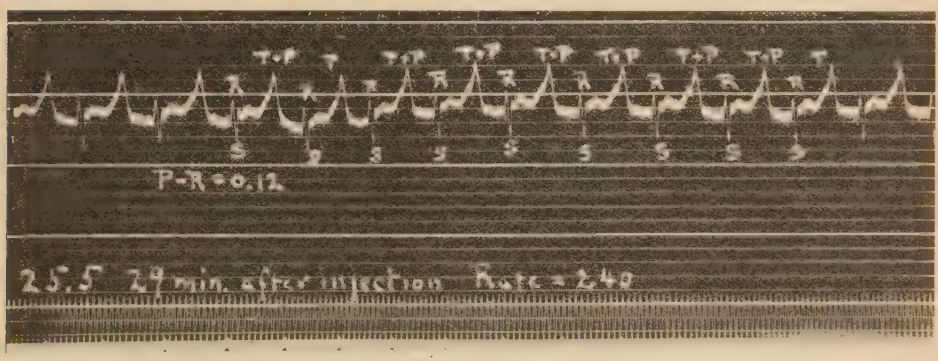

FIG. 9.—Experiment I. Twenty-nine minutes after injection. Normal sequential beat. Conduction time = 0.12 second. Rate = 240. Form of the ventricular complex continues abnormal.

experiment XV, where the vagi were cut (Figs. 4 and 5). The change in the ventricular complexes began three and three-quarter minutes after the injection and was most marked thirteen minutes later. Twenty-two minutes after the injection the ventricular complexes resembled those obtained before the injection.

In two experiments, I and XII, partial auriculoventricular block occurred. In experiment I the vagi were intact. Changes in the ventricular complexes occurred, similar to those seen in experiments XV and XVI. Before the injection the electrocardiograms were normal (Fig. 6). After the injection of serum the conduction (P–R) time gradually lengthened. In a half minute the R-waves became smaller, a splitting and deepening of the S-waves and an increase in the size of the T-waves set in. In three minutes partial block occurred, at first every eighth auricular beat failing

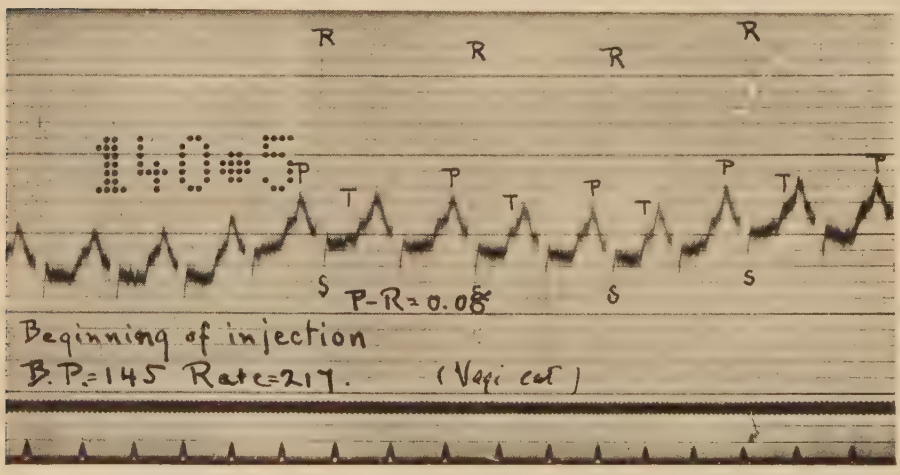

Fig. 10.—Experiment XII. Vagi cut. Beginning of injection. Normal sequential beat. Conduction time = 0.08 second. Blood-pressure = 145 mm. Hg. Rate = 217.

to stimulate a ventricular contraction (Fig. 7). The conduction time after a blocked auricular beat was 0.12 second at first, but it lengthened to 0.14 second five minutes later, when every fifth or fourth auricular beat was blocked (Fig. 8). The partial block continued until twenty-two minutes after the injection, when all auricular contractions were followed by ventricular contractions, the conduction time being 0.15 second. The conduction time gradually improved, and, at twenty-nine minutes after the injection, was 0.12 second (Fig. 9), and the ventricular complexes again resembled those seen before the injection. In experiment XII,

both vagi were cut. Before the injection the blood-pressure was 145 mm. Hg., the rate was 217, the conduction (P–R) time was 0.08

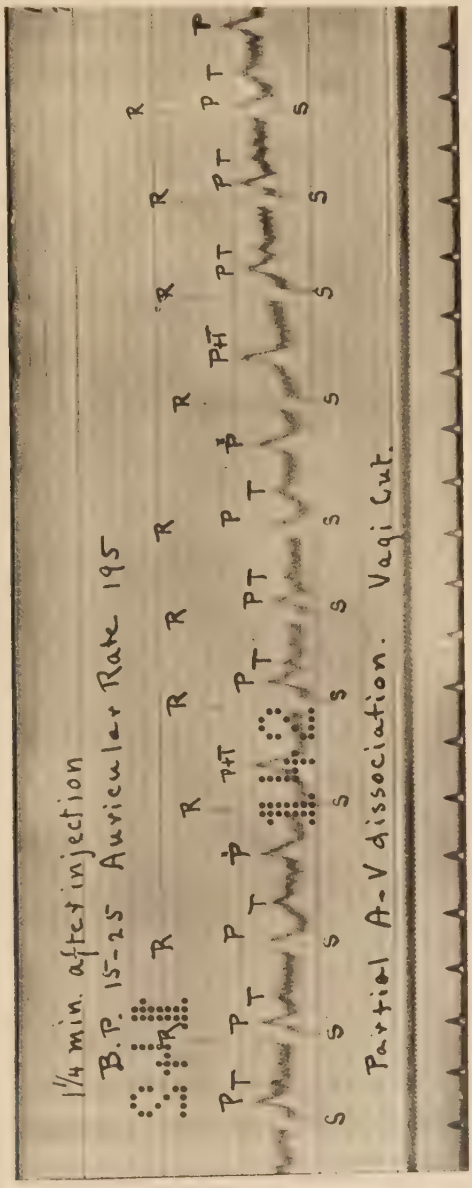

Fig. 11.—Experiment XII. One and a quarter minutes after injection. Partial auriculoventricular dissociation. Blood-pressure = 15 to 25 mm. Hg. Auricular rate = 195. One auricular beat in every five is blocked. Conduction time varies from 0.14 to 0.28 second.

second, and the ventricular complexes were normal (Fig. 10). Thirty seconds afterward, partial auriculoventricular block appeared, when the blood-pressure had fallen to 20 mm. Hg. Fifteen seconds later every fifth auricular beat was blocked (Fig. 11). The conduction (P–R) time in the cardiac cycles following the blocked auricular beats was 0.15 second. In the succeeding cycles it gradually lengthened until it was 0.27 second; then an auricular impulse was again blocked. In spite of the fact that the blood-pressure remained low (10 to 18 mm. Hg.), the sequential beat returned after two minutes. The conduction time at first was 0.20 second (Fig. 12), but five minutes later it was 0.11 second.

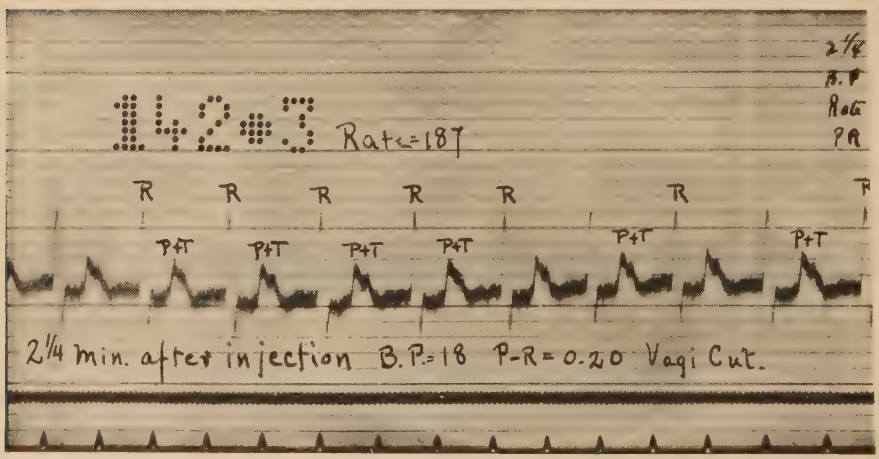

Fig. 12.—Experiment XII. Two and a quarter minutes after injection. Sequential beat. Conduction time = 0.20 second. Blood-pressure = 18 mm. Hg. Rate = 187.

The electrocardiograms obtained in experiment IX showed many unusual changes after the serum injection. Before the injection the blood-pressure was 135 mm. Hg., and the electrocardiograms were normal (rate 210). One minute after the injection, the blood-pressure was 40 mm. Hg. and the rate was 140. There was a definite lengthening in conduction from 0.09 to 0.18 second, lasting only one minute, and then a gradual diminution occurred. In six and one-half minutes after the injection, the P–R time was normal

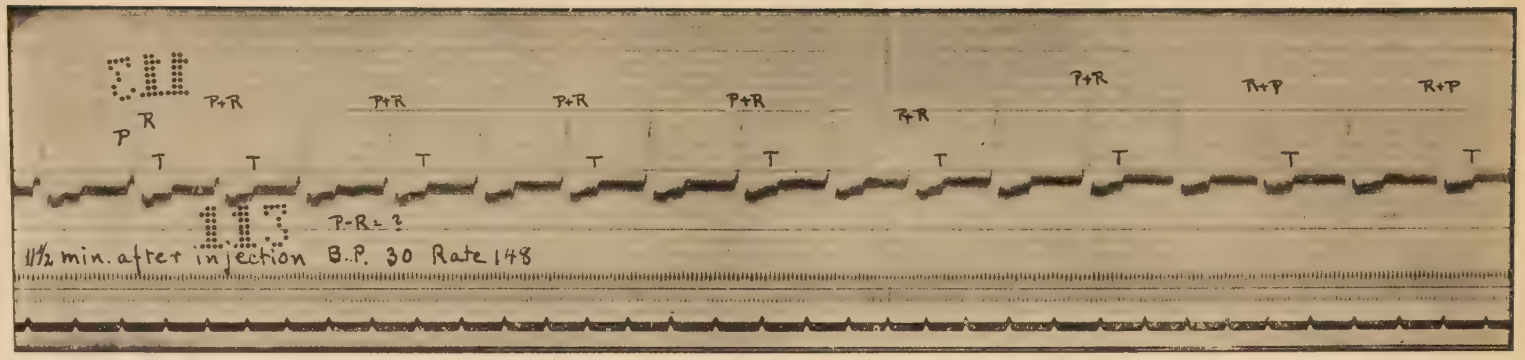

FIG. 13.—Experiment IX. Vagi intact. Eleven and a half minutes after injection. Auricles and ventricles contracting synchronously. Blood-pressure = 30 mm. Hg. Rate = 148.

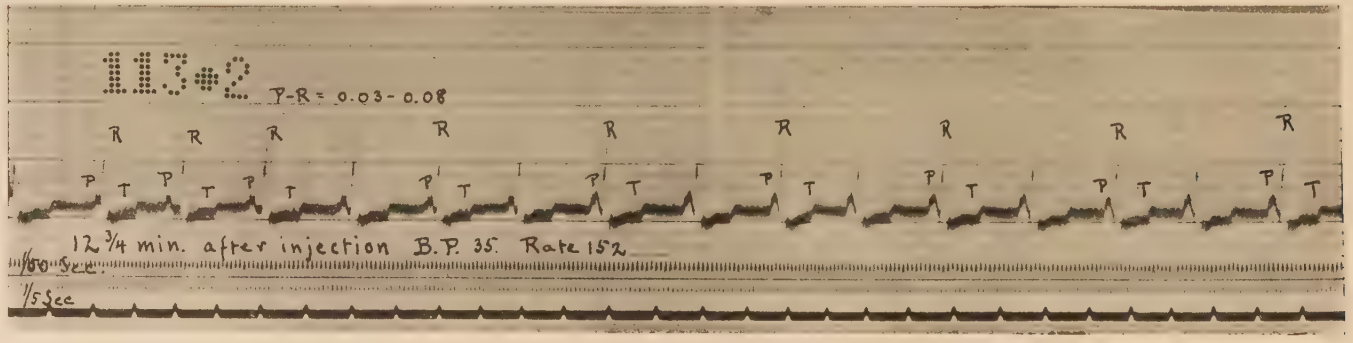

FIG. 14.—Experiment IX. Twelve and three-quarter minutes after injection. Ventricular contractions following auricular contractions after an abnormally short interval. Blood-pressure = 35 mm. Hg. Rate = 152.

again and the cardiac rate was unchanged. Meanwhile, the blood-pressure had fallen further from 40 to 20 mm. Hg. The record

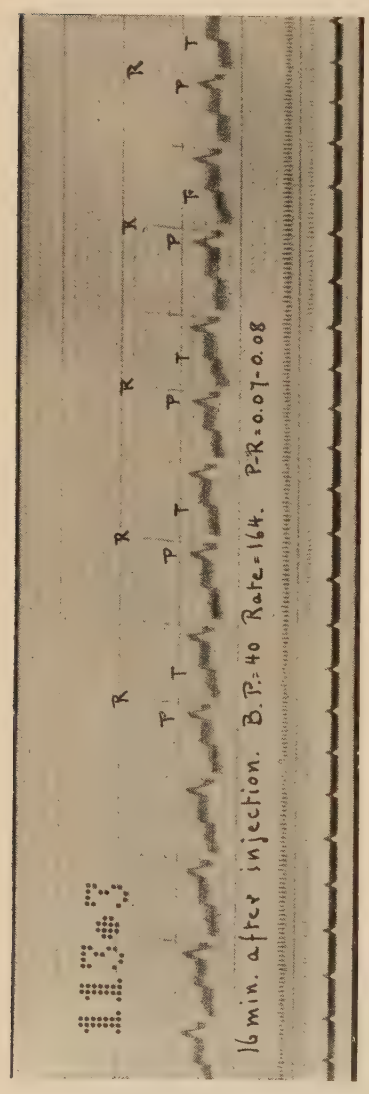

FIG. 15.—Experiment IX. Sixteen minutes after injection. Conduction time = 0.07 to 0.08 second. Blood-pressure = 40 mm. Hg. Rate = 164. Electrocardiograms resemble closely the control curves.

FIG. 16.—Experiment IX. Nineteen and a half minutes after injection. Conduction time = 0.06 second. Blood-pressure = 40 mm. Hg. Rate = 160. The P-wave is inverted.

obtained at eleven and one-quarter minutes after the injection showed that the P-waves and R-waves were practically synchronous

(Fig. 13). One and one-half minutes later, however, the P-waves again preceded the R-waves, but by an interval of 0.03 to 0.08 second, and were partly fused with them (Fig. 14). The P- and R-waves were entirely separated three and one-quarter minutes later, while the blood-pressure had risen again to 40 mm. Hg. (Fig. 15). Nineteen and one-half minutes after the injection, the P-waves had become negative (Fig. 16), and twenty-three and three quarter minutes after the injection, normal complexes were obtained the P–R time being 0.1 second, the rate 167 per minute, and the blood-pressure still 40 mm. Hg. (Fig. 17). From this time on the blood-pressure rose gradually, the rate diminished somewhat, while the conduction (P–R) time showed no further change, and the electrocardiograms continued normal.

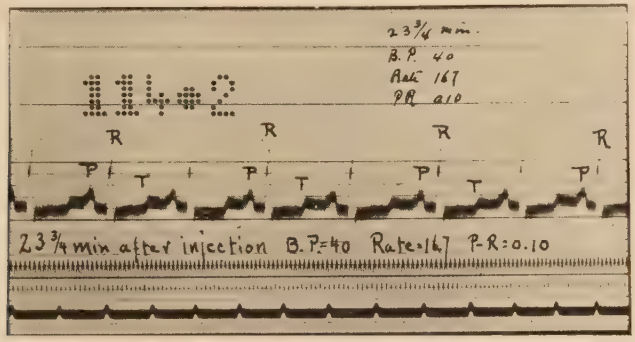

Fig. 17.—Experiment IX. Twenty-three and three-quarter minutes after injection. Conduction time = 0.08 second. Blood-pressure = 40 mm. Hg. Rate = 167. The electrocardiogram resembles closely that obtained before the injection, except that the R-wave is broken and not so high. Before injection blood-pressure = 135. mm. Hg. Rate = 210. Conduction time = 0.09 second.

Discussion. The experiments which have been described demonstrate that during anaphylactic shock, caused by the intravenous injection of horse serum into sensitized dogs, disturbances of the heart-beat may occur which produce definite changes in electrocardiograms. These cardiac disturbances manifest themselves in several ways. The conduction of the stimulus of the heart-beat from auricles to ventricles may be definitely delayed or even occasionally prevented, causing in the electrocardiograms prolonga-

tion of the P–R time or the occurrence of P-waves which are not followed by ventricular complexes. The ventricular contractions may become abnormal, yielding markedly altered ventricular complexes. These changes in the ventricular complexes are well-defined in the electrocardiograms of three experiments and consist of a diminution of the R-waves, a marked deepening of the S-waves and an exaggeration of the T-waves, which become sometimes partly fused with the S-waves. This change in the form of the ventricular portions of the curves was gradual and departed more and more from the normal after the anaphylactic shock until a maximum was reached, and then usually returned gradually to the form obtained before injection. These changes resemble closely those observed by Eppinger and Rothberger[1] in electrocardiograms of dogs, when a 20 per cent. silver nitrate solution was injected directly into the wall of the right ventricle, or when the limb of the atrio-ventricular bundle leading to the right ventricle was cut. When the silver nitrate solution was injected into the wall of the left ventricle, they obtained a distinctly different form of electrocardiogram. It seems evident, therefore, from their experiments, that the side of the heart into which injections are made determines the character of the change in form of the electrocardiogram, specific for the side injected. As the changes in the curves of our experiments always resembled those of Eppinger and Rothberger in which the right side of the heart was injured, it seems possible that in our experiments the ventricular activity was disturbed by damage to the musculature, especially of the right ventricle, or to the path of conduction in the right ventricle. The analogies which can be drawn between their curves and ours offer evidence for the possibility that the right side of the dog's heart is more affected in anaphylactic shock than the left, just as the right side of the rabbit's heart seems to be, as pointed out by one of us.[2] Still further evidence is given by our work on the rabbit during anaphylaxis.[3]

The development of a mechanism unusual in spontaneously

[1] Wien. klin. Woch., 1909, xxii, 1091; also Ztschr. f. klin. Med., 1910, lxx, 1. See also Rothberger and Winterberg, Zentralbl. f. Herzkrankh., 1913, v. 206.

[2] Auer, loc. cit.

[3] Robinson and Auer, loc. cit.

beating hearts has already been mentioned. It occurred in experiment XI (Figs. 13 to 17). The electrocardiograms indicate that the ventricles suddenly ceased to follow the auricles in the normal manner, but that the two parts of the heart contracted synchronously. This continued for several minutes, the auricles contracting either at the same time or very shortly before the ventricles, when the time which elapsed between the onset of auricular and ventricular systoles was not sufficient for the normal passage of the impulse. At first the P-waves had a normal outline, but later the form of the P-waves changed suddenly to a downwardly directed wave. A few minutes afterward the electrocardiogram was again normal.

Such changes in electrocardiograms from the dog have been published by Rothberger and Winterberg[1] (see Figs. 1 and 2 of their paper). After stimulation of the left accelerator nerve, the P-and R-waves gradually approached each other and then became synchronous. Suspension curves of the auricles and ventricles, made simultaneously with the electrocardiograms, show that the auricles and ventricles contracted synchronously. Later on, the normal relation of these waves gradually returned. They interpret this phenomenon, which was observed in a number of experiments, as the result of stimulation of the left accelerator nerve, and believe that the power of stimulus formation in the atrioventricular region is raised by the activity of the left accelerator, so that this region supersedes the normal region as the cardiac pacemaker. Thus atrioventricular autonomy is established, the point of origin of the heart beat gradually shifting from the sino-auricular region to the atrioventricular region. These observations have been repeated and confirmed recently by Ken Kuré,[2] who interprets his findings in a similar manner, although ordinary graphic and not electrocardiographic methods were used.

The phenomenon observed in our experiment is also to be interpreted as resulting from changes in the point of origin of the heart-beat. If the junctional tissue suddenly assumed the function of pace-maker, the auricles and ventricles would contract synchronously, and later, the point of origin having changed to the auricles,

[1] Arch. f. d. ges. Physiol., 1910, cxxxv, 559.
[2] Ztschr. f. Exp. Path. u. Ther., 1913, xii, 384.

the auricular activity would precede the ventricular. The occurrence of the negative P-waves is also accounted for by the junctional tissue as the origin of the heart-beat. This same type of change in the electrocardiogram has been met in our work on rabbits, as will be described elsewhere. It is not possible to say what relation these changes, which began eleven and one-quarter minutes after the injection of the horse serum, had to the anaphylactic reaction. The fact that such changes occurred in the rabbit, in which no anesthetic was used, makes it unlikely that the occurrence

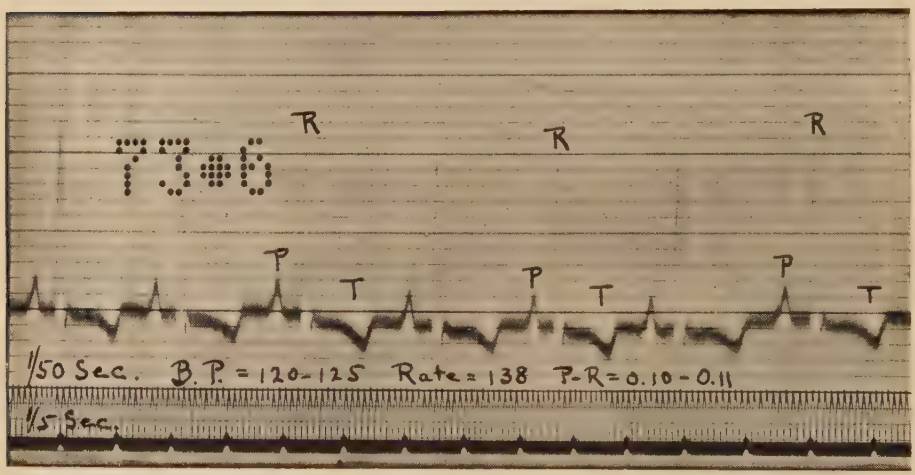

FIG. 18.—Experiment V. Vagi intact. Unsensitized dog. Electrocardiogram at onset of experiment. Conduction time = 0.11 second. Blood-pressure = 120 to 125 mm. Hg. Rate = 138.

of an atrioventricular rhythm was the result of etherization. Nor is it possible to see any definite relationship between its occurrence during anaphylaxis and after left accelerator stimulation.

The possibility that the cardiac disturbances are secondary to the marked fall in blood-pressure must be considered. In order to determine the effect of a sudden lowering of blood-pressure on the electrocardiogram of the dog, three experiments were performed in which the blood-pressure was lowered by intratracheal injections of amyl nitrite, intravenous injections of sodium nitrite, and by cutting both the greater and lesser splanchnic nerves. The experi-

ments were performed under the same conditions as those in which anaphylactic shock was produced, except that non-sensitized dogs were used. As the result of these procedures, rapid changes in

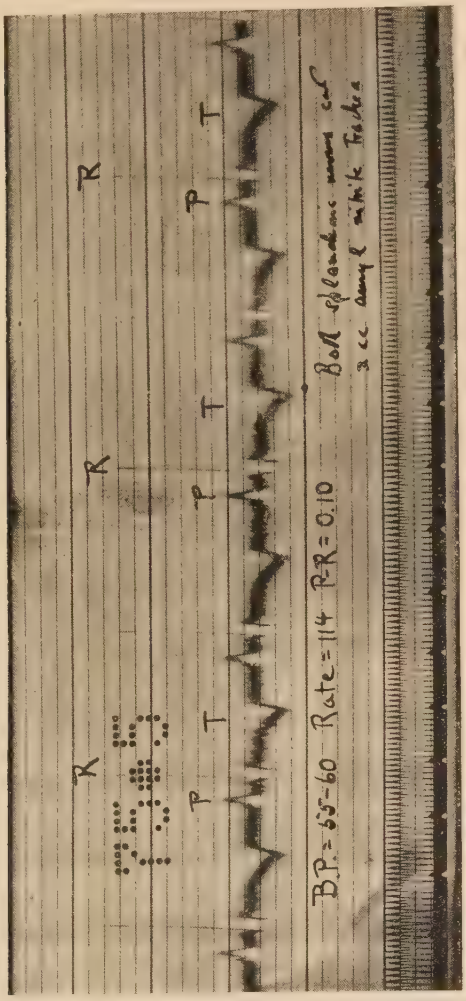

FIG. 19.—Experiment V. After both splanchnic nerves had been cut and 2 c.c. of amyl nitrite injected into trachea. Blood-pressure = 55 to 60 mm. Hg. Rate = 114. Conduction time = 0.10 second. No marked change in form of electrocardiograms following fall in blood-pressure of 65 mm. Hg.

blood-pressure of 60 to 90 mm. Hg. were obtained, without any definite changes in the electrocardiograms. The only change in conduction time, which was observed in these experiments, was a

shortening which sometimes accompanied the fall in blood-pressure, a change opposite to that seen in the positive anaphylactic experiments. The fact that a fall in blood-pressure of 65 mm. Hg. may occur without changing the cardiac mechanism, as indicated by the electrocardiogram, is illustrated by Figs. 18 and 19. Moreover, in several experiments in which anaphylaxis was produced, the drop in blood-pressure was not followed by changes in the electrocardiograms. And when changes were observed, the relation between the fall in blood-pressure and the cardiac disturbances was such as to render it very unlikely that the former was the cause of the latter. Thus in Experiment VIII, the marked delay in conduction which occurred one minute after the injection, returned to normal while the blood-pressure remained at a level even slightly lower than that at which it was when the conduction time was most prolonged (see Chart I). In this experiment and in several others, the heart was beating normally before the rise of blood-pressure commenced. Another curve (Chart II), obtained from Experiment X, will make this lack of relationship between cardiac disturbances and low blood-pressure still clearer. Here the blood-pressure dropped from 155 to 45 mm. within forty-five seconds after the injection of horse serum. Nevertheless, the conduction time rose only from 0.08 to 0.09 second and the electrocardiograms showed no alteration throughout the experiment. This answers an objection which could be made to our interpretation of Chart I; the abrupt drop of blood-pressure and consequent anemia of the heart muscle cannot now be held responsible for the increased conduction time and for the change in the complexes such as Chart I from Experiment VIII shows, because an even greater drop of blood-pressure (Chart II, from Experiment X) affected the conduction time but slightly and the shape of the electrocardiograms not at all. From the facts, therefore, that marked and sudden drops of blood-pressure were not followed by any cardiac changes in some cases of anaphylaxis and in control experiments, and that the abnormalities in the electrocardiograms disappeared in several experiments before there was any rise in blood-pressure, it seems legitimate to assume that the cardiac disturbances were not secondary to lowered blood-pressure, but represent an independent phenomenon of the anaphylactic reaction.

In order to determine whether the central cardiac inhibitory mechanism played any part on the production of the cardiac disturbances of anaphylaxis, both vagi were cut before the injection

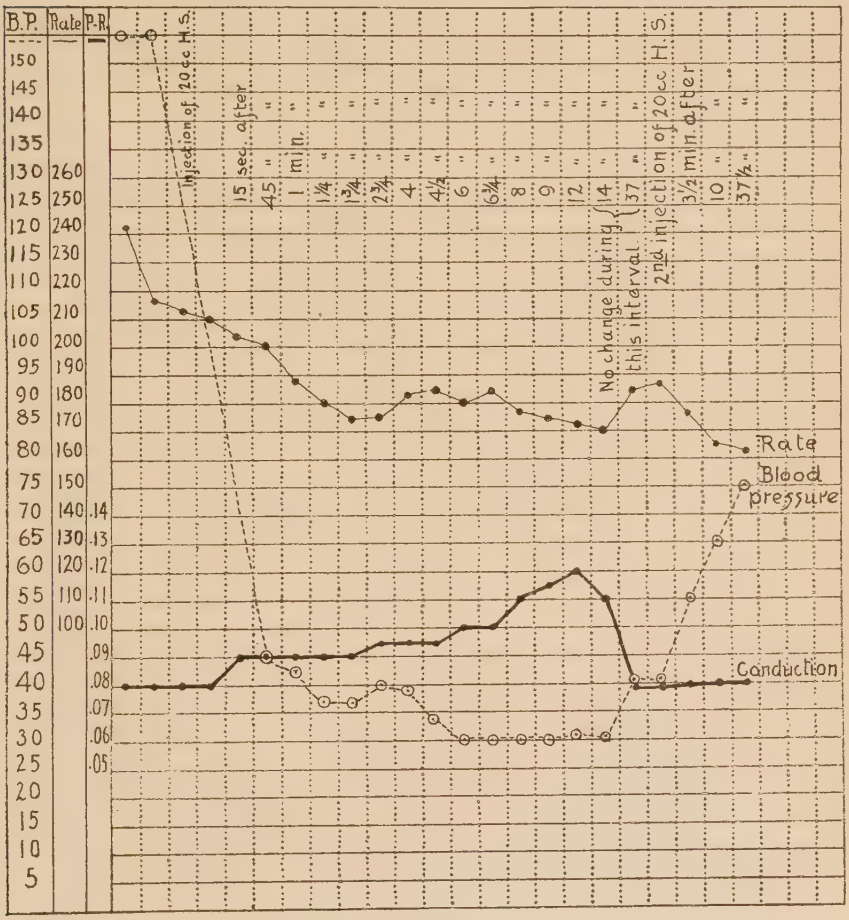

CHART II.—Curve constructed from the records of Experiment X. There were no changes in the shape of the complexes at any time.

of horse serum in four experiments. In addition it seemed advisable to investigate this question, because changes in the heart-beat are produced by certain drugs which resemble those occurring in our experiments and which seem to be caused, at least in part,

through the action of the drug on the vagus centre. The partial dissociation so often seen following the administration of digitalis therapeutically, and the disturbances of the heart-beat which have been observed after the injection of morphine by Einthoven[1] and by Eyster and Meek,[2] disappear after atropine is administered or after the vagi are cut. In our experiments (Nos. XI, XII, XV, and XVII) in which the vagi were cut, the effect of the injection of serum was apparently entirely similar to that observed in the other experiments, where the vagi were intact. In two of these experiments (Nos. XI and XVII) no definite alteration occurred in the heart-beat. In the third, partial heart-block developed (Figs. 10 to 12), while in the fourth, marked changes in the form of the ventricular complexes occurred. These were similar to those seen in other experiments in which the vagi were intact (Figs. 3 and 5). It can be stated, therefore, that the principal changes in the electrocardiograms during the anaphylactic reaction occurred both with the vagi intact and after the vagi had been cut. The central cardiac inhibitory mechanism thus does not play a part in the production of the cardiac disturbances which have been observed in the anaphylactic reaction of the dog.

The action of horse serum itself and ether, as causative factors of the cardiac changes described above, we excluded in control experiments on normal dogs when horse serum was injected or when the blood-pressure was lowered by various means. No changes comparable to those observed during anaphylaxis were observed. We may also call attention to the experiments when horse serum was injected during the state of anti-anaphylaxis, which will be discussed below.

In eight anaphylaxis experiments, the dogs were reinjected with 20 c.c. of horse serum after they had partially recovered from the drop in blood-pressure. None of them showed any effect on the blood-pressure nor on the shape of the electrocardiogram, although the first dose had perhaps caused marked alterations in the form of the complexes, as in Experiments VIII, IX, XIV, XV, and XVI. In these experiments, therefore, each dog served as its own control

[1] Arch. f. d. ges. Physiol., 1913, cxlix, 48.

[2] Heart, 1912, iv, 59.

so far as ether, horse serum and an anaphylactic phenomena are concerned. These experiments show that horse serum and ether *per se* do not cause cardiac disturbances of the kind we have described, and secondly, they demonstrate that these changes are of a true anaphylactic nature, since they are not obtainable during the antianaphylaxis induced by the first reinjection.

An interesting question, which these experiments bring up, is the possible role which these cardiac changes play in the production of the characteristic drop of blood-pressure. It seems to us that the heart does not have a vital action in this respect, for a characteristic blood-pressure effect may be obtained without any derangement of the cardiac beat. Thus Biedl and Kraus' main contention that the heart is negligible as a factor in the causation of the fall in blood-pressure, is probably correct.

The facts outlined above justify us, we think, in concluding that the cardiac changes noted during anaphylaxis in the dog are not of central origin, nor are they secondary to the drop in blood-pressure or to the action of horse serum and ether *per se*, but that they are caused by an action on the peripheral cardiac tissue itself. What this action may be we do not care to discuss at the present time.

Conclusions. Anaphylactic shock in the dog, caused by the intravenous injection of horse serum into sensitized animals, may produce definite cardiac disturbances which are revealed by the electrocardiogram. These cardiac changes consist of disturbances in conduction of the heart impulses, abnormalities in the ventricular contractions and other unusual disturbances of the mechanism of the heart-beat. They come on very quickly after the injection of serum and may be of short duration, and are not obtained during anti-anaphylaxis. They are not the result of the marked fall in blood-pressure which occurs, nor does the central cardiac inhibitory mechanism play a part in their production. These cardiac disturbances apparently are a definite primary expression of anaphylactic shock in the dog. The right ventricle seems to be more affected than the left.

PROTOCOL OF EXPERIMENT VIII. FEBRUARY 15, 1913

Tan and white dog, male, weight 5750 gms. (H. 153). Dog etherized, cannula introduced into trachea and etherization by intratracheal insufflation begun. Electrodes applied to right foreleg and left hindleg.

Time.	Number of curve.	Blood pressure.	Rate.	P–R time.	Form of complexes.
10.34	100.1	..	167	0.10	P well formed, R of 15 mm., definite S, no T-wave.
10.44	Cannulæ in external jugular and in carotid artery.				
10.45	100.2	..	212	0.09	R of 14 mm., S deeper, split T-wave.
10.46 (Fig. 1)	100.3	100	212	0.09	No change.
10.47	Injection of 20 c.c. horse serum into jugular vein begun.				
	100.4	..	207	0.10	No change.
10.48	Injection of horse serum finished.				
	100.5	..	204	0.14	No change.
10.48¼	100.6	25	178	0.14	P-wave smaller, T less definite. Respiration regular.
10.48½	101.1	15	167	0.16	No change.
10.49	101.2	15	170	0.18	S-wave deeper.
10.49¼ (Fig. 2)	101.3	20	161	0.17	No change.
10.49½	101.4	..	163	0.16 to 0.17	No change. Animal quiet
10.50½	102.1	20	165	0.16	R of 8 mm., S 4 mm. deep.
10.51	102.2	..	161	0.15	No change.
10.51½	102.3	15	161	0.14 to 0.15	No change.
10.52½	102.4	15	157	0.13 to 0.14	R of 6 mm. and broken in ascending. Respiration regular, dog quiet.
10.53¼	103.1	10 to 15	158	0.12 to 0.13	No change. Moderately active expiration.
10.54¼	103.2	10 to 15	160	0.11 to 0.12	R of 5 mm., break in ascending limb.
10.55¼	103.3	10	161	0.11	No change. No feces passed
10.56¼	103.4	10	160	0.10	No change. Respiration slower, regular.
10.57½ (Fig. 3)	103.5	10	160	0.09	Respiration slower.
10.59¾	104.1	..	153	0.09	R 7 mm. high, S 3 mm. deep.
11.00	104.2	15	154	0.09	No change.
11.01¼	104.3	15	157	0.09	Double peak of T, less distinct.
11.02¾	104.4	18	156	0.09	No change.
11.04	104.5	18	158	0.085	No change.
11.07	105.1	25	168	0.09	R wave of 8 to 10 mm. Dog quiet.
11.08¼	105.2	30	165	0.09	No change.
11.10¾	105.3	30 to 32	174	..	No change.
11.13¾	105.4	32	174	0.09	No change. Dog on ½ ether.
11.16	105.5	35	180	0.09	No change.
11.19	106.1	40	180	0.09	No change. Dog quiet.
11.22½	106.2	40	180	..	No change.
11.28	106.3	40 to 45	180	0.09	No change.
11.37	..	50			

Time.	Number of curve.	Blood pressure.	Rate.	P–R time.	Form of complexes.
11.40½	106.4	45 to 50	188	0.09	No change.
11.48¼	106.5	45 to 50	190	0.09	No change.
12.04	107.1	55 to 60	188	0.09	No change.
12.05½	107.2	55	185	0.09	R of 10 to 12 mm.
12.06	Injection of 20 c.c. of horse serum begun.				
..	107.3	..	180	0.09	R of 13 mm.
12.07	Injection finished.				
..	107.4	..	177	0.09	No change.
12.07¼	107.5	55 to 60	..		
12.08	107.6	55 to 60	182	0.085 to 0.09	No change.
12.13	108.1	55 to 60	185	0.09	No change.
12.14	108.2	55 to 60	180	0.09	No change.
12.24½	..	55	..	..	Ether stopped. No change.
12.25	108.3	55	187	0.09	No change.
12.30	108.4	45 to 55	186	0.08 to 0.09	No change.

Wound dressed after removal of cannulæ and after treating wound with tincture of iodine. Dog removed to kennel, but was found dead on February 17, two days after the experiment.

DISCUSSION

Dr. W. G. MacCallum: I would like to ask several questions:

1. Is there after these experiments any morphological change in the bundle?
2. What is the course of the lowered blood-pressure?
3. Is there any way of elevating the pressure after it is once depressed?

Dr. Auer: Hemorrhages were found in the conducting system of the dog which succumbed; the number of observations at my disposal are small, however, and I cannot discuss this more fully just now.

There are ways of raising the blood-pressure; barium chloride will increase the pressure very successfully, as Biedl and Kraus have shown.

ABSCESS OF THE LIVER FOLLOWING TYPHOID FEVER

By ROBERT B. PREBLE, M.D.
CHICAGO

It has been fifteen years since the subject of abscess of the liver as a result of typhoid fever has been discussed by this Association. At that time Da Costa, in a paper upon "Jaundice in Typhoid Fever," briefly discussed the subject upon the basis of 22 collected cases. Since that time the number of records has slowly grown, so that in 1911, von Eberts was able to report upon 30 cases. In his article in the *American Journal of the Medical Sciences*, one can find a review of the literature. Since this article there is but one item in the *Index Medicus*, an article in a Japanese journal, unavailable because printed in Japanese.

When one thinks of the often extensive ulcerations in the intestines, occurring in typhoid fever, and the direct vascular connection between the ulcers and the liver, it is surprising that abscesses of the liver are so extremely rare. There are no very accurate data existing upon which to base an opinion as to the frequency of this sequel; 12 in 2000 fatal cases in the Hölscher statistics; 1 in 677 clinical cases collected by Romberg; 10 in 927 cases by Dopfer. Personally, I have seen only the one instance of abscess of the liver, which furnishes the basis for this report, in a typhoid experience covering not far short of 1500 cases.

The difficulties of estimating the relative frequency of these abscesses is further increased by the fact that cases have been included which do not properly belong here. Thus, Curschmann reports one in which the abscess of the liver was part of a pyemia, resulting from a decubitus in a patient who had typhoid. Several of the cases reported by Legrand and included in the 30 tabulated by von Eberts are certainly open to question. Indeed, if one

requires the demonstration of the typhoid bacillus in the pus, the cases are reduced to 12 in number, 8 cases of pure infection and 4 in association with various staphylococci and streptococci.

It appears to me that these two groups of cases, one the pure typhoid infection and the other a mixed infection, are essentially different in nature. In the first group it is not necessary to assume that there is anywhere any break in the vascular system; that nowhere is there a primary infected thrombosis with secondary infarction of the liver. All that is necessary is to assume that in some one or more of the small areas of necrosis frequently found in the liver the typhoid bacillus has taken on pyogenic properties.

In cases where there is a mixed or pure infection with the common types of pyogenic cocci one must account for their presence by the assumption that somewhere infective thrombosis has occurred. This may be of one of the primary ulcerations in the small intestines, a secondary abscess in the region of the appendix, or an abscess in a mesenteric gland, or the point of origin may be remote from the portal system, as may be illustrated by the pyemia following decubitus. One would also expect that in some cases the abscess of the liver has followed infection of the biliary passages and such instances have been recorded.

Patient, J. M., male, aged thirty-nine years, entered hospital November 11, 1911, with temperature of 106°; pulse 120, and respirations 20. He had been feeling badly for some days, malaise, generalized muscular pains, headache, repeated nose-bleed, nausea, and vomiting. Shortly before entrance he had a sudden severe pain in lower portion of right side of chest.

At entrance the examination, aside from the high temperature, showed an enlarged spleen; distended abdomen; liver enlarged, about four inches below costal border, with tension of the abdominal walls in this region and great pain and tenderness. No thorax findings except moderate, evenly diffused bronchitis. Blood showed a polymorphonuclear leukocytosis of 17,500, positive Widal, and a growth of typhoid bacilli was obtained from the blood.

A diagnosis of typhoid fever with cholecystitis was made.

The patient ran an ordinary, moderately severe course, presenting no peculiarities except for a continued, though gradually falling, leukocytosis, and for the fact that for days the liver continued swollen and tender. Later the tenderness disappeared, although the liver remained enlarged, but at no time was there any jaundice.

After thirty days the temperature returned to normal and remained so, with the exception of occasional slight rises up to the date of discharge; that is, for twenty days. During this period the convalescence presented no peculiarities except that the liver remained enlarged about two fingers below the arch, and was at times painful, and the leukocytosis persisted at about 10,500. On January 6, 1912, the patient had gained sufficiently to permit of his going home, but after being home one week returned because of increasing discomfort in the liver region. The temperature was normal, but the white count had gone up to 22,000. The enlargement of the liver had further increased. A diagnosis of liver abscess was made and he was laparotomized by Dr. A. E. Halstead. The abscess was found in the right lobe of the liver, about one-half inch from the surface, containing eight to ten ounces of creamy, yellow pus, entirely free from any admixture of bile. From the pus a pure growth of typhoid bacilli was obtained.

The subsequent course to recovery was uneventful, and the patient was discharged entirely well in six weeks.

The clinical picture of the liver abscess following typhoid does not differ essentially from that of any other liver abscess. During the course of the typhoid or after a longer or shorter period of apparently established convalescence the attention will be drawn to the liver region by pain, by a sense of fulness, discomfort, and tension. Some pain is a fairly constant symptom, but varies greatly in its severity, duration, and character. It presents no distinguishing peculiarities.

Fever is a normal part of the picture, but varies in height, character, and duration. In general, it is of a septic type, but it may be continuous or regularly intermittent. It may be continuous with the typhoid temperature, or there may be a more or less prolonged fever-free interval, lasting days to months.

Chills are often encountered. In many of the reports no definite statement is made, so that the relative frequency is unknown, but they often occur. It should be noted that there is no necessary relation between the infective agent and the presence or absence of chills. Thus some cases in which typhoid bacilli only were found in the pus, frequent chills occurred, while in others showing an admixture of streptococci there were no chills throughout the course of the disease.

Enlargement of the liver is practically constant, but varies

greatly in degree from one scarcely demonstrable to massive enlargements. It may be upward or downward, depending upon the site of the abscess, which if large may cause both upward and downward enlargement.

Jaundice has been seen a number of times, in 16 per cent. of the cases, and it is interesting to note that this is just the frequency of jaundice in single abscesses of the liver, irrespective of the cause. In other words, jaundice is neither more nor less common in typhoid abscess of the liver than in other forms, and this in spite of the frequency with which the bile tracts are infected by the typhoid bacilli.

Just as the abscess may compress the common duct, so it may compress the portal vein, causing ascites, although it does this very rarely.

To these direct results of the abscess may be added others resulting from perforation into various viscera, the peritoneum, colon, or some other portion of the gastro-intestinal tract, or more frequently upward, through the diaphragm, into the pleural cavity or lung. All of these things have happened.

Spontaneous recovery may occur through rupture and drainage of the abscess into the bowel. Death may be precipitated in a variety of ways.

The treatment is, of course, surgical, and does not differ from that of any other liver abscess. Puncture, whether done for purposes of exploration or treatment, is dangerous, and of six cases treated in this way all died. Of 14 cases treated by free opening and drainage, whether by laparotomy or thoracotomy, 12 recovered.

TABLE I

EXOPHTHALMIC GOITER, PAGE 60 A, YEAR 1912

Indicate amount of gland involved by common fraction. Describe all encapsulated tumors in *red* in the upper part of the case space, and all other tissues in black in the lower part.

MACROSCOPIC

	Identification Data							Operations				Diagnosis	
	Office No.	Hospital No.	Name	Address	Sex	Age	Weight Kilos Height Centimeters	First Date and Character	Second Date and Character	Third Date and Character	Amount of each lobe removed R-Rt. L-Lt. I-Isth.	Immediate with corrections in red	
1													
2													

.....GOITER, PAGE.....B, YEAR.....

MICROSCOPIC Indicate amount of gland involved by common fraction. Describe all encapsulated tumors in *red* in the upper part of the case space, and all other tissues in black in the lower part.

	Vessels		Stroma			Acini			Parenchyma Cells								Secretion			Diagnc
	Size of Smaller Bloodvessels 1. Diminished 2. Normal 3. Increased 4. Dilated	Size of Smaller Lymphatics 1. Diminished 2. Normal 3. Increased 4. Dilated	Amount in Walls of Acini 1. Reduced 2. Normal 3. Increased 4. Great Increase	Inflammatory Changes 0, 1, 2, 3, 4	Degeneration H-Hyaline Ct-Cartilage M-Myxomatous Cl-Calcareous 0, 1, 2, 3, 4	Size of Cavity 0-None 1-Small 2-Medium 3-Large 4-V. Large	Shape T-Tubular lumenless S-Spherical lumenless N-Spherical lumen Normal I-Irregular P-Papillæ 1, 2, 3, 4	Microcysts (Distended Single or Joined Acini) Size 0, 1, 2, 3, 4	Size 0-Embryonic 1-Atrophy 2-Normal 3-Hypertrophy 4-Very Marked Hypertrophy	Number 1. Reduced 2. Normal 3. Hyperplasia 4. Marked Hyperplasia	Shape S-Sperical (Embryo.) Cb-Cuboid (Normal) Cl-Columnar (Hypertrophy) F-Flattened (Pressure) 1, 2, 3, 4	Cytoplasm Cl-Clear G-Granular V-Vacuolated Cd-Colloid 1, 2, 3, 4	Nucleus size of 1. Shrunken 2. Normal 3. Swollen 4. Fragmented	Nucleus staining Reaction 1. Feeble 2. Normal 3. Intense 4. Irregular	Mitosis 0, 1, 2, 3, 4	Cytolysis 0, 1, 2, 3, 4	Amount 0, 1, 2, 3, 4	Density of Staining Reaction 0-No Stain 1-Feeble 2-Moderate 3-Marked 4-Intense	Granular Contents A-Amorphous C-Crystalline E-Epithelium 0, 1, 2, 3, 4	Histolog
1																				
2																				

	Weights in Grams			General Characteristics							
Total of all tissue removed	Encapsulated Tumors	Removed Gland Tissue outside of encapsulated Tumors	Entire Gland Estimated weight outside encapsulated Tumors	Consistency 1.-Very Soft 2.-Soft 3.-Firm 4.-Hard	Roughness of Outer Surface 0-Smooth 1. 2. 3. 4.	Capsule 0-V. Thin 1-Thin 2-Medium 3-Thick 4-V. Thick	Hemorrhage 0. 1. 2. 3. 4.	Degeneration H-Hyaline Ct-Cartilage Mx-Myxomatous Cl-Calcareous 0, 1, 2, 3, 4	Cyst Size of 0-None 1-Small 2-Medium 3-Large 4-V. Large	Bloodvessels Size of Larger 1. 2. 3. 4.	
											1
											2

Final Path.		Chemistry			Summary				Diagnosis of Clinical Condition			Prognosis	Office No.	
	Class	Amount of Iodine per Gram of Dry Gland	Acetonitril Reaction of Gland Tissue	Acetonitril Reaction in Blood	Index of Total Parenchyma per Kilo Body-weight	Index of Total Function	Index of Excretion	Index of Total Circulating Secretion	Stage of Toxic Symptoms 0, 1, 2, 3, 4	Severity of Toxic Symptoms 0, 1, 2, 3, 4	Severity of Second-ary Changes 0, 1, 2, 3, 4	RT-Relief of Toxic Symptoms 0, 1, 2, 3, 4 RS-Relief of Secondary Symptoms 0, 1, 2, 3, 4		
														1
														2

made in 1908, I was able to show that pathologically there were two distinct types of glands to be found among thyroids removed from toxic goitre cases. While purposely avoiding as much as possible previously used technical terms, I attempted to simplify our conception of the pathology by pointing out that the essential element in a large percentage of the cases was an increase in the amount of working tissue—parenchyma cells—within the previously formed acini, or, in other words, hypertrophies, hyperplasias, and regenerations, while in a smaller percentage of the cases, there was an apparent increase in the amount of working tissue—parenchyma—due to an increase in the number of acini, or, in other words, adenomas and adenomatoses, etc. Class I, containing the hypertrophies, hyperplasias, and extreme regenerations, constituted 79 per cent. of the total number of specimens examined, while Class II, containing the fetal and colloid adenomas, the adenomatoses and the so-called simple colloid thyroids, constituted 21 per cent. of the specimens examined.

In comparing my theoretical estimate of the stage and severity of the disease as indicated by the above data with the clinical facts as previously observed and noted by Plummer, it was shown that a direct relationship existed between the apparent functional activity of the gland and the stage and severity of the clinical symptoms. In reviewing the clinical data of his more recent cases, Plummer[1] has found that practically all, if not all, of the cases of clinically true exophthalmic goitre lie in the pathologic groups showing hypertrophy and hyperplasia, while the toxic non-exophthalmic cases are scattered among the other pathologic groups. We have, however, up to the present time, continued the ordinary method of listing clinically all severe toxic goitre cases closely resembling exophthalmic cases[2] on the "exophthalmic goitre" list, while on the "simple goitre" list are placed those cases in which there are slight or no acute toxic symptoms. Our "exophthalmic goitre" list therefore contains those cases coming to our clinic which are ordinarily diagnosticated exophthalmic goitre but which Plummer divides clinically into two classes, exophthalmic toxic and severe non-exophthalmic (*i. e.*, non-hyperplastic) toxic.

[1] Plummer, Amer. Jour. Med. Sci., 1913, cxlvi.

[2] Loc. cit.

I have recently reviewed all the gross and microscopic fixed tissues at hand from the cases reported in 1908, and, in addition, have studied grossly and microscopically in fixed tissues all the glands available which have been removed between May 10, 1908, the date of my previous report, and January 1, 1913, from all patients on our "exophthalmic goitre" list. This includes a total of 1208 thyroids from patients all of whom had shown marked toxic symptoms though not all of whom, in the light of our present clinical knowledge, would now be diagnosticated true exophthalmic goitre. In addition to these 1208 glands from toxic cases, I have similarly studied the glands removed during the year 1912 from cases grouped clinically as "simple goitres," 585 in all. These latter 585 thyroids are from patients presenting very slight or no acute toxic symptoms. I have further studied the thyroids from a number of human embryos and from children, adolescents, and adults, coming to autopsy without clinical history of thyroid derangement. My observations on the latter groups will be presented in later papers.

In order to maintain a standard of comparison in the analyses of these cases, it has been found necessary to adopt numerical equivalents for amount, size, degree, etc., and the analytical data thus designated has been tabulated on forms parallel in size and arrangement of names with those used by Plummer for the tabulation of the clinical data. The headings of the tables are shown in Table I.

All pathologic observations have been made wholly independently of the clinical observations and not compared with the latter until the entire series was completed.

While many thyroids may each present a great variety of histologic pictures, yet a careful examination of a large number of sections from blocks of fixed tissue from different areas combined with the examination of the gross specimens permits one to classify the glands with considerable definiteness. In grouping the specimens, I have classified them with but slight change on the basis which I adopted in 1908 and elaborated last year.[1] Thus groups A, B, C, and D represent Class I, namely, the parenchymatous

[1] Wilson, Northwest Medicine, Seattle, Wash., 1913, v, 1 to 5.

hypertrophies and hyperplasias and extreme regenerations, while groups E, F, G, and H represent Class II, namely, the "adenomas," "adenomatoses," and "colloid goitres."

Hypertrophy and hyperplasia are almost always intermingled, but it is possible to subdivide the hypertrophies and hyperplasias into three classes: Group A, early primary parenchymatous hypertrophy and hyperplasia (see Fig. 1); group B, active advanced primary parenchymatous hypertrophy and hyperplasia (see Fig. 2); and group C, regressing primary parenchymatous hypertrophy and hyperplasia (see Fig. 3). I have used the term "primary" in each of these classifications because I believe it represents a stage of hypertrophy and hyperplasia developing in parenchyma which previously has not been markedly atrophic. Group D contains those specimens in which a marked regeneration of parenchyma is found developing on apparently previously atrophic parenchyma lining the walls of previously distended, colloid-filled, acini (see Fig. 4). This regeneration is marked by the presence of numerous minute acini lined with low, spherical or cuboidal epithelium and filled quite early with densely staining colloid. Critically considered, the process is really a form of hyperplasia and it is possible indeed for it to progressively grade over into primary hypertrophy and hyperplasia, but I have rigidly excluded from groups A, B, and C all glands which did not show marked infolding of acinar walls lined with columnar epithelium. On the other hand, it is frequently impossible to draw the line between those degrees of regeneration in a colloid thyroid which might fairly be presumed to be the cause of toxic symptoms and those in which no effect can be noted. All that I have attempted here is to note, in a study of the glands removed from known toxic cases, the presence or absence of *marked* regeneration. While theoretically it would seem to be extremely confusing to differentiate secondary regenerations from primary hypertrophies and hyperplasias, yet, as a matter of fact, when sections from material which has been properly fixed and stained are studied the task is not a difficult one.

Of the groups in Class II, group E contains the actively growing, non-degenerating fetal adenomas (see Fig. 5); group F contains fetal adenomas which show any of the several types of degener-

ation—myxomatous, hyalin, calcareous, etc. (see Fig. 6); group G contains those definitely encapsulated adenomas whose acini

FIG. 1.—Photomicrograph of a section of thyroid. × 120. Type A. Early primary parenchymatous hypertrophy and hyperplasia. From a case of clinically early true exophthalmic goitre.

FIG. 2.—Photomicrograph of a section of thyroid. × 120. Type B. Advanced primary parenchymatous hypertrophy and hyperplasia. From a case of clinically severe true exophthalmic goitre.

FIG. 3.—Photomicrograph of a section of thyroid. × 120. Type C. Regressing primary parenchymatous hypertrophy and hyperplasia. From a case of clinically true exophthalmic goitre; late stage.

FIG. 4.—Photomicrograph of a section of thyroid. × 120. Type D. Secondary regeneration of atrophic parenchyma. From a case of clinically toxic non-exophthalmic goitre.

are too large to be classified as fetal and which may or may not be degenerated (see Fig. 7); and group H contains those thyroids

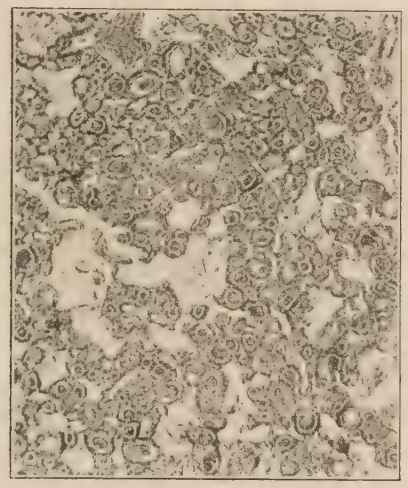

FIG. 5.—Photomicrograph of a section of thyroid. × 120. Type E. Fetal adenoma. From a case of clinically toxic non-exophthalmic goitre.

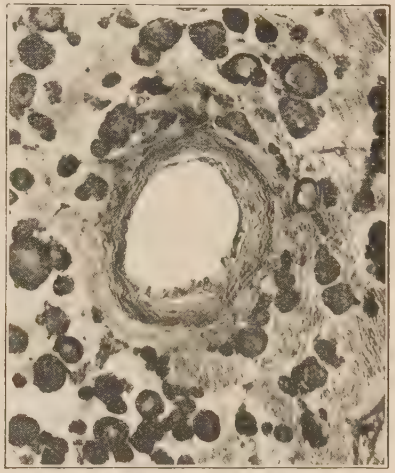

FIG. 6.—Photomicrograph of a section of thyroid. × 120. Type F. Degenerating fetal adenoma. From a case of clinically toxic non-exophthalmic goitre.

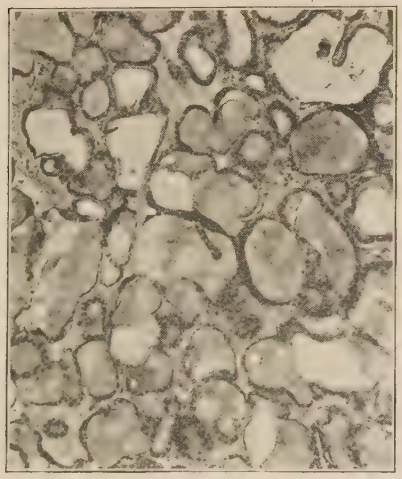

FIG. 7.—Photomicrograph of a section of thyroid. × 120. Type G. Adult, "colloid" adenoma. From a case of clinically toxic non-exophthalmic goitre.

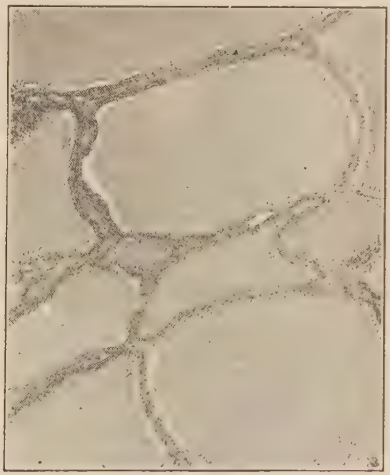

FIG. 8.—Photomicrograph of a section of thyroid. × 120. Type H. "Colloid thyroid." From a case of clinically non-toxic goitre.

not included in the previous classes, many of which, though not presenting definitely encapsulated tumors, yet are composed of more or less segregated groups of acini presenting a picture which, following Adami's lead, I prefer to class as "adenomatoses" (see Fig. 8).

The following table gives the classification of the thyroids studied according to the above grouping.

TABLE II.—PATHOLOGICAL CLASSIFICATION OF THYROIDS FROM PATIENTS ON "EXOPHTHALMIC GOITRE" LIST FROM JANUARY 1, 1905, TO JANUARY 1, 1913, AND OF THYROIDS FROM PATIENTS ON "SIMPLE GOITRE" LIST FOR 1912.

		"Exophthalmic Goitre" List.									"Simple Goitre" List.	
	Years . . .	1905	1906	1907	1908	1909	1910	1911	1912	Totals	1912	
A	Early primary parenchymatous hypertrophy and hyperplasia.	...	1	4	2	1	3	15	6	32 3%	..	A
B	Advanced primary parenchymatous hypertrophy and hyperplasia.	4	26	35	41	44	68	108	89	415 34%	1	B
C	Regressing primary parenchymatous hypertrophy and hyperplasia.	7	21	44	55	46	78	107	140	498 41%	3	C
	Total hypertrophy and hyperplasia (A + B + C).	11 69%	48 83%	83 68%	98 69%	91 71%	149 77%	230 81%	235 89%	945 79%	4	
D	Secondary regeneration of atrophic parenchyma of "colloid" goitre.	1 6%	3 5%	24 20%	24 17%	17 13%	30 15%	20 7%	14 5%	133 11%	50 9%	D
E	Fetal adenomas.	1	3	7	17	8	2	12	2	52 4%	35	E
F	Degenerating fetal adenomas.	3	3	5	3	5	12	21	10	62 5%	101	F
G	Adult ("colloid") adenomas.	...	1	1	...	6	1	...	3	12 1%	128	G
	Total adenomas (E + F + G).	4 25%	7 15%	13 11%	20 14%	19 15%	15 7%	33 12%	15 6%	126 10%	264 44 %	
H	Atrophic parenchyma ("colloid") thyroids, "adenomatoses," etc.	...	...	1	...	1	2	...	...	4	259 44 %	H
	Malignant tumors.	...	...	...	...	...	...	...	...	..	8 1½%	
	Total number of thyroids	16	58	121	142	128	196	283	264	1208	585	

A study of the table reveals the following interesting points:

1. Approximately four-fifths, 79 per cent., of all thyroids from patients who had exhibited sufficiently severe acute toxic symptoms to warrant the clinician in placing them on the "exophthalmic

goitre" list, showed marked hypertrophy or hyperplasia or, more usually, both.

2. During the year 1912 this percentage rose to 89. At the same time a parallel examination by the same observer of 585 thyroids from patients on the "simple goitre list for 1912 showed but four cases—less than 1 per cent.—with hypertrophy and hyperplasia. Of these four cases, three were children and one was a young adult female whose lack of toxic symptoms can be accounted for only on the hypothesis that she was highly resistant and had not yet had time to be affected.

3. During the years 1911 and 1912, every patient diagnosticated clinically as true exophthalmic goitre and on whom thyroidectomy was done, furnished thyroid tissue which pathologically was placed in the groups marked A, B, or C, that is, showing primary parenchymatous hypertrophy and hyperplasia.

4. So far as can be determined, none of the 133 patients—11 per cent.—whose thyroids showed only secondary regeneration of atrophic parenchyma would now be classified clinically according to Plummer as true exophthalmic goitre. This distinction is clinically sharp and positive for the years 1910, 1911, and 1912, and not yet critically reviewed from the clinical standpoint for the preceding years.

5. The statement in paragraph four is equally true for the 130 cases—10 per cent.—whose thyroids are grouped as E, F, G, or H (adenomas, etc.).

6. At the same time, these groups D, E, F, G, and H—regenerations, adenomas, colloids, etc. –contain 97 per cent. of all thyroids removed from patients on the "simple goitre" list for 1912.

In attempting to estimate from the pathologic data alone the stage of the toxic clinical symptoms, the following factors have been taken into account: (1) Age of the patient; (2) weight of the portion of gland removed; (3) character of the bloodvessels; (4) amount of stroma; (5) size and shape of the acini; (6) amount of hypertrophy and hyperplasia of the parenchyma cells, and (7) amount and density of the secretion contained within the acini. These factors must all be considered in estimating the product and output of the gland so far as may be made from a

pathologic examination of the tissues. A careful consideration of all these factors has been made in each case examined and a tentative estimate given of the stage and severity of the disease at the time the patient was operated on. These estimates have been compared in parallel columns with the clinical estimates made by the examining physician for all cases operated on during 1910, 1911, and 1912 (the only years for which the full clinical data—except of those given in my paper of 1908—have as yet been critically reviewed). The results may be briefly summarized as follows:

1. Of the 24 cases diagnosticated pathologically as group A (*early* primary parenchymatous hypertrophy and hyperplasia), 21 (87.5 per cent.) had exhibited symptoms for but three months or less.

2. Of the 265 cases placed pathologically in group B (*advanced* primary parenchymatous hypertrophy and hyperplasia), 11 (4 per cent.) gave a history of toxic symptoms for but three months, 155 (58 per cent.) from three months to one year, 34 (13 per cent.) (almost all young individuals) slightly over a year but with a ligation shortly preceding thyroidectomy, while 65 (24.5 per cent.) (these again almost all young individuals) had exhibited symptoms for over a year and had had no ligation previous to thyroidectomy.

3. Of the 325 cases diagnosed pathologically as group C (*regressing* primary parenchymatous hypertrophy and hyperplasia, 8 (2 per cent.) gave a history of but three months' duration of symptoms (and without ligation prior to thyroidectomy), 25 (8 per cent.) gave a history of one year or less duration of symptoms (and without ligation prior to thyroidectomy), while the remainder, 292 (90 per cent.) gave clinical histories of more than one year duration or had had a ligation some weeks before the performance of thyroidectomy.

Thus it will be seen that, notwithstanding the inaccuracies of patients' statements as to the duration of symptoms, notwithstanding the confusing factor of a ligation previous to thyroidectomy, and notwithstanding the difficulties of correctly estimating the total function from an anatomic study of but a portion of a gland, the fact remains that the stage of true exophthalmic goitre can be

estimated with considerable accuracy from the pathologic data alone in about 80 per cent. of all cases examined.

In attempting to estimate the *severity* of the toxic symptoms in the cases with true exophthalmic goitre, all of which had shown pathologically some stage of hypertrophy and hyperplasia in the thyroid (groups A, B, or C), the same factors were taken into consideration as those entering into the estimate of the *stage* of the disease. A careful consideration of these data resulted in the classification of the cases for 1910, 1911, and 1912 into the four grades of severity: (1) very mild; (2) moderate; (3) severe, and (4) very severe. On only 542 cases out of the 614 was it possible to make a definite comparison of the estimated severity from the pathologic standpoint with the severity as noted by the clinician just prior to thyroidectomy.

Out of these 542 cases, 29 were estimated pathologically as "1" or of "mild" severity. 22 out of the 29 had been previously similarly grouped by the clinician, or, in other words, the pathologic estimate agreed with the clinical findings in 76 per cent. of the cases in this group.

Of the 306 cases estimated pathologically as "2" or of "moderate" severity, 235 were similarly placed by the clinician, an agreement of 77 per cent. in this group.

Of the 166 cases estimated as of severity "3," that is "severe," 117 were similarly grouped by the clinician, or an agreement of 70 per cent.

Of the 41 cases estimated pathologically as severity "4," that is "very severe," 33 have been similarly grouped by the clinician, or 80 per cent. of agreement.

Thus of the 542 cases on which the degree of severity was estimated from the examination of pathologic specimens, such estimate agreed with the clinical estimate in 407 cases, or a total pathologic accuracy of 75 per cent.

Conclusions. 1. A detailed pathologic study of fixed tissue preparations from 1208 thyroids, removed from patients whose condition would ordinarily have been diagnosticated exophthalmic goitre, showed that 79 per cent. of the thyroids contained large areas of marked primary hypertrophy and hyperplasia. A parallel

clinical study has shown that for a period of three years all cases with true exophthalmic goitre, and from whom gland tissue was removed, fall into this list.

2. In the above series of 1208 so-called "exophthalmic goitres" plus 585 so-called "simple goitres" or a total of 1793 thyroids, but four instances of marked primary hypertrophy and hyperplasia of the parenchyma have been noted in cases which did not show clinical symptoms of true exophthalmic goitre. Three of these four patients were children.

3. 21 per cent. of the 1208 glands studied were either regenerations or adenomas. Clinically, while all of these were markedly toxic, all were chronic and none of them would now be grouped clinically as *true* exophthalmic goitre.

4. By assuming that the symptoms of true exophthalmic goitre are the results of an excretion from the thyroid gland and by attempting to determine the amount of such excretion from the pathologic data, one is able to estimate in a large series of cases the clinical stage of the disease with about 80 per cent. of accuracy, and the clinical severity of the disease with about 75 per cent. of accuracy.

5. *It would therefore appear that the relationship of primary hypertrophy and hyperplasia of the parenchyma of the thyroid gland to true exophthalmic goitre is as direct and as constant as is primary inflammation of the kidney to the symptoms of true Bright's disease.* Any considerable finding to the contrary I believe to indicate either inaccurate or incomplete observations on the part of the pathologist or clinician or both.

THE CLINICAL AND PATHOLOGICAL RELATIONSHIP OF SIMPLE AND EXOPHTHALMIC GOITRE

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Up to January 1, 1909, 1004 operations had been done on 966 cases of goitre at St. Mary's Hospital. A brief review shows that we were classifying the cases as simple and exophthalmic goitre. We recognized that a considerable percentage of cases of so-called simple goitre had constitutional symptoms. Whether or not the cases having constitutional symptoms were placed on the simple or exophthalmic list depended upon how closely the clinical complex approached the well-known picture of Graves' disease.

Wilson, in 1908, after reviewing the available pathological material from the cases that had been diagnosed exophthalmic goitre, pointed out that 80 per cent. of the glands showed hyperplastic changes, and that in general the length and severity of the case history could be pointed out from the pathological findings. While it was impossible to overlook the fact that the tissue removed from the majority of patients having a well-developed picture of Graves' disease was hyperplastic, we could not come definitely to the conclusion that this evidence of activity on the part of the thyroid was a constant finding in exophthalmic goitre so long as 20 per cent. of the cases so diagnosed did not show this change in the thyroid.

At about this time a review of the clinical histories and pathological findings of the entire series listed as simple and exophthalmic goitres led to the following tentative conclusions: (1) that at least two distinct but similar types of thyroid intoxication, one associated with non-hyperplastic goitre the other with hyper-

plastic or hypertrophic thyroid; (2) that exophthalmos should be noted only in cases having hyperplastic or hypertrophic thyroids; (3) that the failure of our statistics to show the above conclusions was due largely to the following errors: (*a*) accepting the clincial findings and diagnoses of exophthalmic goitre for all cases placed on the exophthalmic goitre list; (*b*) accepting the pathological findings from only a portion of one lobe of the thyroid; (4) that the clincial errors were attributing the tremor, tachycardia, etc., of neurasthenia, cardiovascular, and nephritic diseases to the thyroid and noting the existence of exophthalmos when only a Stellwag's sign and naturally prominent eyes are associated with the thyrotoxicosis of non-hyperplastic goitre.

I have from time to time pointed out in discussions statistical data bearing out the above conclusions but have refrained from publication until going into a wealth of confusing detail to explain the apparent exceptions is unnecessary.

In writing the histories of the 3207 cases that have come to operation since January 1, 1909, forms were used covering the points which might later prove of interest. Figures and signs, having, in so far as possible fixed values, have been used in place of descriptive adjectives. Observations of fact and opinions were carefully distinguished. The clinical and pathological findings were placed in parallel columns without any comparison of notes on the part of the clinicians and pathologists. This made possible the complication of statistics by clerks who are not in any way warped by preconceived ideas or a knowledge of factors other than those under immediate consideration.

The term thyrotoxicosis is here applied to the constitutional state associated with goitre. As a matter of convenience for quickly presenting the association of the clinical and pathological findings, the constitutional symptoms accompanying goitre were attributed to a toxemia the result of a disturbed thyroid function. As a temporary expedient the cases were classified pathologically as hyperplastic and non-hyperplastic, and clinically as hyperplastic toxic, hyperplastic atoxic, non-hyperplastic toxic, and non-hyperplastic atoxic. The glands showing marked hypertrophy were included with the hyperplastic goitres. Following this

classification for the 2917 new cases coming to operation between January 1, 1909, and January 1, 1913, 42.8 per cent. were hyperplastic and 57.2 per cent. were non-hyperplastic. Of the hyperplastics 99.2 per cent. were toxic and 0.8 per cent. were atoxic. Of the non-hyperplastic 23.3 per cent. were toxic and 76.7 per cent. were atoxic.

While the association of the constitutional symptoms with non-hyperplastic goitre was to a certain extent a personal equation, this was to a limited degree true for the cases having hyperplastic thyroids. The estimation that 23.3 per cent. of the non-hyperplastic goitres were toxic was made on a very conservative basis.

Patients coming under observation with non-hyperplastic toxic goitre gave a history of having first noted the goitre at the average age of 22 years, and the evidence of intoxication at the average of 36.5 years. The corresponding ages for hyperplastic goitre were respectively 32 and 32.9 years.

That non-hyperplastic goitre was noted ten years earlier in life than hyperplastic goitre, that 14.5 years elapsed between the appearance of non-hyperplastic goitre and the development of notable toxic symptoms and that the constitutional symptoms were noted but a few months later than the goitre in the patients affected with hyperplastic thyroid was alone sufficient to show that we were dealing with, at least, two distinct pathological and clinical groups. That one was not the sequence of the other is self-evident.

Are all hyperplastic goitres coming to operation toxic? Throughout the series the number of cases in which the clinician failed definitely to note and attribute constitutional symptoms to the thyroid, and which were later diagnosed by the pathologists hyperplastic thyroid, vary from two cases in 1909 to four cases in 1912. Two of these four cases were in children under four years of age and could be excluded in considering the hyperplasia of adults. The third case was a girl, fifteen years of age, who gave a history of having noticed the goitre, periods of tremor, tachycardia, and palpitation for nine months. However, these symptoms were not attributed to the thyroid previous to operation. The fourth case was a woman, forty-seven years of age, who gave a history of having noticed the goitre for twelve years, rapid growth during the few months previous to coming to operation and a long train of symp-

toms, part of which might be attributed to thyroid intoxication. A few cases that had small areas of hyperplasia in the thyroid were excluded because they were still under discussion by the pathologists. The majority of them had moderate toxic symptoms, indicating that the activity of the thyroid was proportionate to the degree of the hyperplasia.

Is hyperplasia of the thyroid more prevalent in the first two decades of life than we have definite knowledge of, perhaps indicating a thyroid activity in response to some demand that cannot be considered far from normal? If so, is this hyperplasia of the thyroid to be sharply distinguished from the hyperplasia associated with Graves' disease, which develops at the average age of thirty-two? I do not believe these questions can be definitely answered at the present time, though there is much evidence suggesting an affirmative answer, at least to the clinical side of the question.

Is the exophthalmos of thyrotoxicosis always associated with hyperplastic goitre? The pathological reports fail to show the presence of hyperplasia in the cases in which exophthalmos was noted by the clinician six times in 1909, four times in 1910, twice in 1911, and not in a single instance in 1912. Nine hundred and eleven new cases of goitre came to operation in 1912. In most of the exceptions to the rule, previous to 1912, we were able definitely to prove that there was an error in noting the presence of exophthalmos.

Should all toxic hyperplastic goitres be included under the term, exophthalmic goitre? Possibly there is a small group of cases which should not be included. However, that there is a small chance for error in answering this question in the affirmative if we include only those cases coming to operation is indicated by (1) the cases having diffuse hyperplasia of the thyroid coming under observation from one to three, three to six, six to nine, nine to twelve, twelve to eighteen, eighteen to twenty-four months and over two years from the onset of toxic symptoms respectively, 50, 59, 67, 75, 80, 80, and 87 per cent. had exophthalmos (questionable cases excluded); (2) if we select from any periods in our series twenty-five consecutive patients having hyperplastic thyroids and mild toxic symptoms over 50 per cent. have exophthalmos,

and if we select from the total number of patients coming to operation during 1911 and 1912 the twenty-five cases of non-hyperplastic thyroids having the most intense intoxication exophthalmos is not noted in a single instance. It is quite possible that exophthalmos may be associated with non-hyperplastic toxic goitre, but, if so, it is so rare that it must be in a way considered accidental.

Is the symptom complex accompanying hyperplastic goitre to be directly attributed to disturbed thyroid function? While it has been so considered in this paper only as a matter of convenience for pointing out the association of the clinical and pathological findings and while I do not wish to enter into a discussion of this subject at the present time, I wish to call attention to a point in support of this theory that, so far as I know, has not hitherto been made, viz., that an individual aged twenty-two years with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the symptom complex associated with hyperplastic thyroid that the best trained diagnosticians are constantly confusing the two conditions.

Can we associate the symptom-complex of non-hyperplastic toxic goitre with any definite pathological change in the thyroid? For the present this question must be answered in the negative.

Correlating the above statistical data, we may safely come to the conclusion that exophthalmic goitre is a definite clinical complex always associated with hyperplasia of the thyroid and that it should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goitre. Still more interesting and convincing is the correlation of a mass of detail with the data given here. This involves too much for a short paper. However, a general conception of the clinical pictures accompanying non-hyperplastic toxic and exophthalmic goitre is given as an introduction to the paper by Drs. Blackford and Sanford.[1]

For the purpose of quickly presenting the clinical pictures, let us note the parallelism of thyrotoxicosis and alcoholism and assume that there are three toxic elements in the thyroid secretions, one

[1] "A Demonstration of a Depressor Substance in the Serum of the Blood in Exophthalmic Goitre," read before the Association of Am. Phys., May, 1912.

damaging chiefly the nervous system, one the circulatory system, and the other producing exophthalmos. In exophthalmic goitre all three elements are in excess, but the clinical picture is dominated by a nerve toxin, although in individual cases the circulatory toxin or element producing exophthalmos may seem to be in excess.

The intoxications from non-hyperplastic goitre may be divided into two merging groups: (1) a group in which the cardiac toxin predominates, in which the clinical picture closely resembles and in many instances cannot be differentiated from the cardiovascular complex resulting from alcoholic, luetic, septic, and other well-known toxins; (2) a group more closely approaching the picture of Graves' disease and including the cases that have been erroneously so diagnosed by the mass of the profession.

The average lapse of time between the appearance of non-hyperplastic goitre and toxic symptoms is 14.3 years. That the patient comes under observation three years later indicates that the onset is usually insidious. Nervousness, tremor, loss of strength and weight, as a rule, develop slowly, but may appear suddenly long before definite evidence of myocardial damage. The administration of iodine may cause the sudden appearance of those symptoms with myocardial insufficiency such as might follow the prolonged drinking bout of an old toper who had not previously shown decided evidence of chronic alchoholism. In some cases the clinical aspect, as noted above, closely approaches that of exophthalmic goitre. However, the symptoms are less complex, less definitely associated, and except for a damaged heart, less intense. There is much evidence to suggest that during the 14.5 years previous to the onset of definite toxic symptoms many of the cases of non-hyperplastic thyroid may be compared to the alcoholic tippler in that if the soil is right they develop arteriosclerosis, in many cases showing the combined picture of thyrotoxicosis and arteriosclerosis.

The development of a typical syndrome of Graves' disease in a case having a definite history of simple goitre means that a hyperplastic goitre has been superimposed upon the simple type.

The onset of exophthalmic goitre is, as a rule, relatively acute and the course of the disease fairly definite. The clinical picture early in the history is that of a toxin acting directly on the more

vital organs, more notably the central nervous and vascular systems. Later it is made more complex by the interaction of those organs whose functions have been directly disturbed by the toxin. The order of onset of the most important symptoms based on the average of our series is as follows: (1) cerebral stimulation, (2) vasomotor disturbances of the skin, (3) tremor, (4) mental irritability, (5) tachycardia, (6) loss of strength, (7) cardiac insufficiency, (8) exophthalmos, (9) diarrhea, (10) vomiting, (11) mental depression, (12) jaundice, and (13) death.

If the average course of the intoxication be represented by a curve the greatest height is reached during the latter half of the first year, and then suddenly drops to the twelfth month. In many instances it reaches the normal base line during the next six months. More often it fluctuates with periods of exacerbation for the next two to four years. Secondary symptoms and exophthalmos may remain, but the active course only rarely continues over four years without distinct intermissions. Compare the striking resemblance of the character, order of onset, and course of this train of symptoms with that resulting from the heavy use of alcohol by a susceptible individual over a corresponding period of time. Near the crest of the curve any shock, operation, etc., that treats the patient to another drink may result in delirium tremens or death.

In the average course after the first year the symptoms that may be attributed to long-continued intoxication rather than to a high degree of acute intoxication, *i. e.*, those from the more chronic types of heart, liver, and degeneration of the kidney, enter strikingly into the clinical picture. In attempting to construct a composite curve we find that the curves for those symptoms that we can readily attribute to a high degree of immediate intoxication from the thyroid gradually drop, while the curves for those findings attributable to a long-continued intoxication of a lower degree gradually rise.

In a later paper I will point out that there is much evidence to suggest that the sudden onset of the toxic symptoms is preceded by a period during which the patient is gradually habituated to the disturbed function of a developing hyperplastic thyroid and that

following the disappearance of the clinical manifestations of the intoxication the patient is still taking care of the products of an overactive gland, and if this overactivity with or without clinical manifestations continues sufficiently long in an individual prone to arterial degeneration, arteriosclerosis, with secondary contracted kidneys, high arterial tension, etc., will ultimately develop. The picture of thyrotoxicosis from both hyperplastic and non-hyperplastic goitres may be compared to that from alcoholism in its various degrees and manifestations, varying with the dose, length of administration, and susceptibility of the individual.

While the weight of the evidence seems to indicate that, whatever the primary cause, the symptom complex of exophthalmic goitre is directly attributable to hyperplasia of the thyroid, I wish to repeat that I have so considered it in this paper only as a matter of interest and convenience in associating the pathological and clinical findings.

A DEMONSTRATION OF A DEPRESSOR SUBSTANCE IN THE SERUM OF THE BLOOD OF PATIENTS AFFECTED WITH EXOPHTHALMIC GOITRE

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During the past year we have conducted a series of experiments with a view to throwing further light on the relation of the secretion of the thyroid to exophthalmic goitre. We have studied chiefly the cardiovascular effects on the dog of intravenous injections of sterile non-hemolytic blood-serum from nervous individuals and from patients affected with exophthalmic goitre. Also, numerous saline extracts of goitre have been injected intravenously into dogs and the effects on the blood-pressure studied.

Gley,[1] in 1911, announced that the serum of certain cases of exophthalmic goitre produces marked cardiac depressor action. He showed, too, that a first injection of potent exophthalmic serum conferred a tolerance of such a nature that subsequent injections of the same serum during the same experiment produced little or no effect.

We have attempted to follow out Gley's researches, injecting intravenously into dogs the serum procured from patients affected with exophthalmic goitre. The effect on blood-pressure was recorded graphically on a long paper kymograph in the usual manner, using the left carotid artery for the arterial cannula. All injections were made into the right femoral vein. The right vagus was

[1] Jour. de Phys. et de Path. Gén., 1911, xiii, 928 to 941; Cleret, ibid., pp. 955 to 970.

exposed and stimulated by induction shock in certain experiments. Blood was obtained by sterile technique from the median basilic veins of the patients, collected in sterile flasks and the serum allowed to separate in the cold. The manifest difficulty that must always be encountered in such work, *i. e.*, the impracticability of obtaining a large supply of blood from each case, has somewhat hindered certain experiments, but we believe that our results are sufficiently interesting to justify reporting.

Gley states that 5 c.c. of serum per kilo dog weight must be used to obtain the best results. We did not have sufficient serum for such large dosage, but obtained excellent results with smaller doses. We have injected $2\frac{1}{2}$ to 4 c.c. serum per kilo dog weight as an average dose, and except when stated to the contrary, this has been the amount of serum.

We have used for these experiments the sera from twenty-eight patients having exophthalmic goitre. Other sera examined have included those from normal individuals, from patients having goitres, without apparent intoxication, and from patients presenting the picture of a long-standing intoxication, presumably due to adenomas of the thyroid. Only the sera from patients with active symptoms of exophthalmic goitre and with markedly hyperplastic glands, as shown by microscopic examination, have produced in the dogs injected any definite symptoms of cardiovascular depresssion.

The curves produced by the sera from patients affected with exophthalmic goitre have naturally fallen into three groups:

Group I. Those sera causing more than 30 mm. of Hg. drop in blood-pressure.

Group II. Those sera causing a drop in blood-pressure but less than 30 mm. of Hg.

Group III. Those sera causing no appreciable drop in blood-pressure.

The significance of this classification was observed only after an analysis of the individual cases.

Group I. *Six Sera Causing Drops in Blood-pressure of More than* 30 *mm. of Hg.* The four curves in Chart I (*a*), all of which produced drops in blood-pressure of more than 30 mm. of Hg. when injected in doses of 2.5 c.c. per kilo dog weight, were obtained by

injecting sera from patients who were at or near the height of an early and severe intoxication, as shown by the following summaries of the case histories:

Case 69,123.—Female, aged twenty years. Three months before (March, 1912) noticed suddenly all the typical cardiac, nervous, and muscular symptoms of Graves' disease. Rapid progress during one month to acute vomiting, with great loss of strength. During the third month vomiting ceased, but all other symptoms were marked. (Experiment conducted on dog 253.)

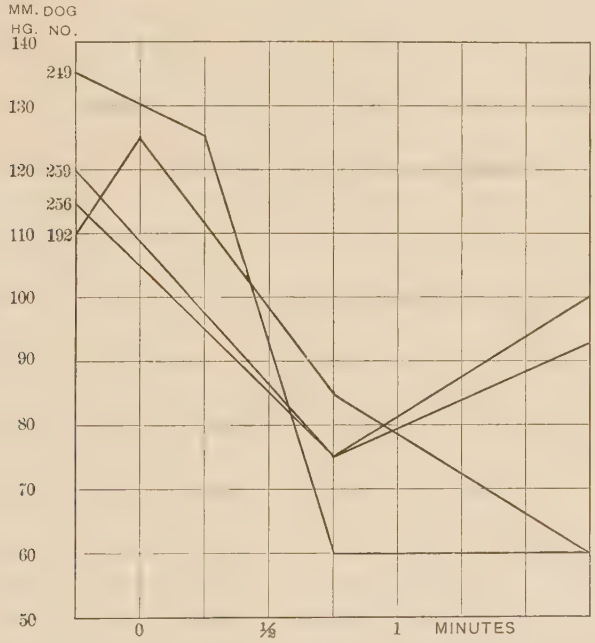

Chart I (*a*).—Drops in blood-pressure of more than 30 mm. after injection of sera from patients in the stage of acute intoxication from exophthalmic goitre.

Case 69,198. —Female, aged fifty years. Slight goitre noted one year before (May, 1911). Definite typical symptoms of exophthalmic goitre began six months before with loss of weight, weakness, and nervousness. Two months before violent crisis, with vomiting, the patient remaining in an acute condition for one week, since then vomiting in spells. In bed most of the time. Loss of

thirty pounds in weight in two months. Patient had not noted exophthalmos, which was moderately evident. (Experiment conducted on dog 259.)

Case 67,993.—Male, aged seventeen years. Three months before (February, 1912) began to lose weight, and all the usual symptoms became evident and rapidly progressed. A month later goitre was noted and the patient forced to bed by weakness. In bed one month, then slight improvement, and has been able to be out of bed the past month, though a marked intoxication is still present. (Experiment conducted on dog 249.)

Case 68,628.—Female, aged twenty-three years. Six months before (January, 1912) developed nervous and cardiac symptoms and exophthalmos. She rapidly became worse, and at present shows marked intoxication. Diarrhea for one month. Marked loss of strength and fifteen pounds loss of weight. This patient died in an exacerbation following a single ligation. Unfortunately autopsy on this patient was refused. (Experiment conducted on dog 192.)

We believe these histories show conclusively that the four cases were all acute and severe intoxications. Clinical diagnoses in these as well as the following cases have been confirmed by pathological examination of the goitres except the one which terminated fatally.

The two cases shown in Chart I (*b*) are interesting exceptions. One was a fairly acute intoxication of only moderate severity; the other was a chronic intoxication of marked severity. The case histories are as follows:

Case 75,496. Male, mulatto, aged thirty years. Past history, gonorrhea, syphilis (positive Wassermann), and some alcoholic excess. Two years before (November, 1910) began to lose weight and strength, and noticed nervous, cardiac, and eye symptoms. Rapid progress to an extreme crisis, with prostration, vomiting, and diarrhea. Then recovery during six months; able to do some work, but still had marked intoxication with a chronic diarrhea. Weight forty pounds below normal. (Experiment conducted on dog 361.)

Case 69,619.—Female, aged nineteen years. Nine months before (October, 1911) had to stop school on account of weakness,

dyspnea and nervousness. Symptoms progressively worse until forced to bed six months before. After a rest she improved steadily, and presents a clean-cut but not marked picture of exophthalmic goitre. (Experiment conducted on dog 264.)

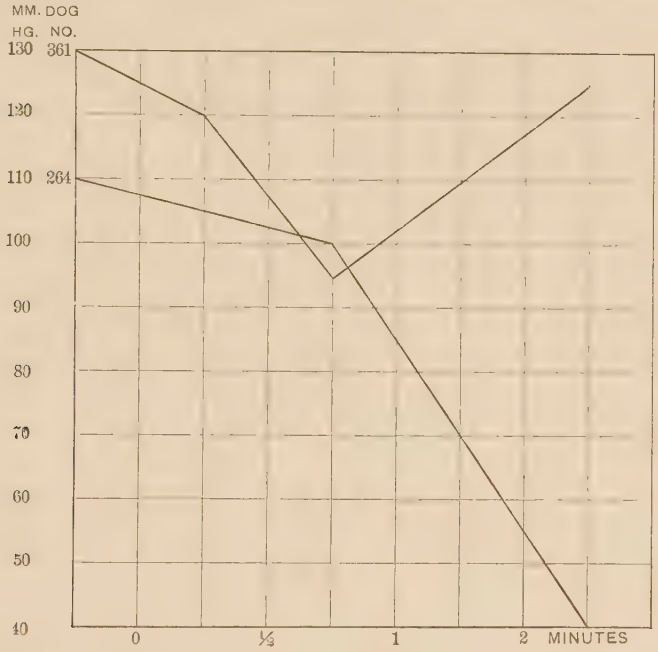

CHART I (*b*).—Drops in blood-pressure of more than 30 mm. after injection of large doses of sera from patients with moderate intoxication from exophthalmic goitre.

From the two preceding histories we may judge that neither case was extreme. On examining our records we find that the doses of serum given each dog were about three times that used to secure the marked effects shown in Chart I (*a*). Again, we may note that the first case (75,496) was a chronic and severe one, but gave only a 35 mm. drop in blood-pressure, thus almost admitting it into the next group. The second case (69,619) gave a marked fall in blood-pressure, and though not very severe, was not far past a crisis when the blood was taken.

Group II. *Ten Sera Causing Drops in Blood-pressure of Less than 30 mm. of Hg.* Chart II shows the curves resulting from

injections of six of these sera which cause a fall in blood-pressure of less than 30 mm. of Hg., but which apparently contained a slight amount of the depressor agent. Eight of these ten patients had been afflicted with the disease for more than a year and none of them seemed near any marked exacerbation. In general it may be stated that these cases were of longer standing and with more pronounced intoxication than those in the following group. Two typical histories from this group are as follows:

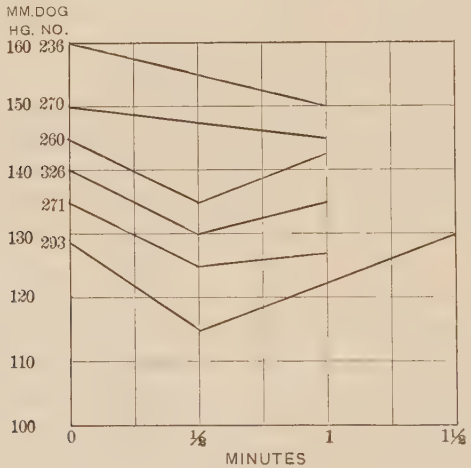

CHART II.—Drops in blood-pressure of less than 30 mm. after injection of sera from patients not at the height of intoxication from exophthalmic goitre.

CASE 68,883.—Male, aged thirty years. Appendectomy had been done eighteen months before (January, 1910), following which symptoms of exophthalmic goitre promptly appeared and progressed during six months to an extreme intoxication with vomiting, diarrhea, and prostration. Loss of forty pounds in six months. For the past six months steady improvement, and now is nearly normal in weight, though still affected with definite Graves' disease. (Experiment conducted on dog 253.)

CASE 67,283.—Female, aged thirty-six years. Tremor noted for several years. Always more or less nervous. Increased irritability and gradual loss of strength was noted six months before (November, 1911). No dyspnea. Slight diarrhea during the

past month. Working steadily to date. (Experiment conducted on dog 236.)

Thirteen Sera Causing no Appreciable Drop in Blood-pressure. Chart III shows six curves as typical of the thirteen inert sera which fall into this group. None of the patients seemed to be near a crisis, and eight of them had been sick less than nine months.

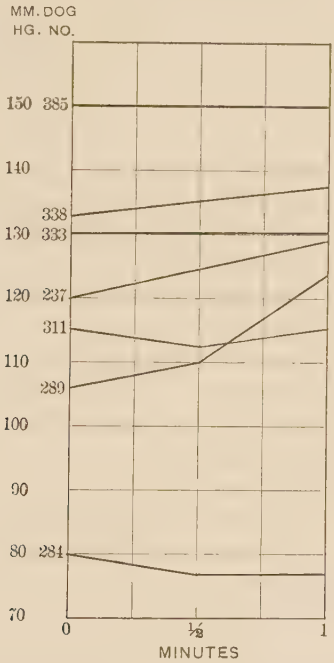

CHART III.—No effect on blood-pressure following injection of sera from patients with symptoms of intoxication from exophthalmic goitre, but not at or near crisis.

These experiments seem to indicate that patients affected with exophthalmic goitre who are suffering from a marked degree of intoxication at or near the height of the clinical curve of the disease (Plummer) possess serum which has a powerful depressor action. The authors have failed to demonstrate this depressor action by similar means in normal sera, or in sera from patients not having markedly hyperplastic thyroids. Also sera from patients with

exophthalmic goitre not at or near the crest of the wave of intoxication are less potent or may be entirely inactive.

Since it was not always thought best to bleed very sick patients, only a small number of experiments have been made with sera from patients with severe intoxications. Yet it may be of interest to know that most of the patients that were bled experienced considerable relief from their subjective symptoms after the bleeding.

The results of intravenous injections into dogs of saline extract of ninety goitres of various kinds from human patients have also been studied. These experiments may have some bearing on the action of the depressor sera and a brief report of the results is herewith appended.

Intravenous Injections of Saline Extracts. Experiments with extracts of forty-eight exophthalmic thyroids have shown that the markedly hyperplastic goitres considered typical of Graves' disease have a more powerful depressor action than that of the extract of any normal organ examined, including muscle, liver, spleen, pancreas, breast, testicle, thyroid, etc. The fall in blood-pressure averages 60 mm. of Hg., and is often considerably more, whereas that from other tissues in any comparable dosage is usually less than 25 mm.

Extracts of adenomas of the thyroid, of simple colloid goitres, and of normal thyroids likewise have a depressor action, which, however, has not been found so marked as that produced by extracts of exophthalmic thyroids. Injections equivalent to as much as 5 gm. per kilo dog weight do not cause a fall as great as that of the extracts of exophthalmic goitres in doses of 0.5 gm. per kilo dog weight.

The first injection of any extract of fresh goitre, as of most extracts of tissue, confers a marked degree of tolerance to subsequent injections of the same material during the same experiment.

As is well known, peptone solutions cause a marked fall in blood-pressure on intravenous injection, and subsequent injections show that a tolerance has been established similar to that produced by extracts from goitres. The depressor action of peptone solution is not, however, affected by a previous dose of the extract of exophthalmic goitre, nor is the action of the extract of exophthalmic goitre affected

by a previous dose of peptone solution. On the other hand, it is interesting to note that the depressor action of the extract of an exophthalmic goitre is much diminished by a previous dose of potent serum from a case of toxic exophthalmic goitre, and the reverse, judging from a limited number of experiments, is equally true. In other words, a crossed tolerance seems to exist between the depressor action of extract of exophthalmic goitre and of exophthalmic serum. It seems probable, therefore, that the depressor agent in the extract of exophthalmic thyroid and that in the serum from a case of exophthalmic goitre are of the same nature.

No attempt has yet been made to identify the chemical nature of the depressor substances in these extracts of thyroids or of those in sera of patients affected with exophthalmic goitre. From certain experimental evidence it seems that the substance is neither cholin nor ordinary peptone.

Conclusions. We believe that the work submitted justifies the following conclusions:

Fresh extracts made from exophthalmic thyroids contain a powerful depressor substance.

A powerful depressor substance likewise exists in the sera obtained from certain cases of exophthalmic goitre.

The latter substance is present in direct proportion to the clinical acuteness and severity of the disease.

The sera from patients with non-hyperplastic thyroids do not have a depressor action.

After an active depressor dose of the serum from a case of exophthalmic goitre the depressor action of the extract of an exophthalmic goitre is weakened or abolished. The converse is also true.

DISCUSSION

Dr. V. C. Vaughan: With respect to the conclusions of the last paper, the truth is that all protein poisons lower the blood-pressure in dogs; but most of them have a different effect on guinea-pigs, in which animals such injections cause constriction of the bronchioles. I would like

to ask what is the cause of the fall of blood pressure? Is it due to dilatation of the capillaries? Does barium chloride prevent it? Does nicotine affect it? The general results of the experiments would seem to indicate that there is a degenerating protein responsible for the phenomena noted.

Dr. Frank Billings: From a clinical standpoint, it must be admitted that the blood pressure is increased in the active stage of exophthalmic goitre, meaning by this that the heart's action is increased; at the same time there is a dilatation of the cutaneous vessels, independent of the arterial tension.

Dr. G. H. Whipple: Blood serum from eclamptic patients will produce sharp and prolonged depression of blood pressure in dogs; I believe there is present in such blood a toxic substance due to the splitting of protein.

Dr. A. J. Ochsner: The findings of Dr. Wilson and those of Dr. Plummer correspond. Since Dr. Wilson's first paper on this subject, I have examined regularly all specimens coming to our laboratory without any knowledge of the clinical history of the cases from which the specimens were derived, and my experience quite confirms Dr. Wilson's findings.

Carrying out the ideas expressed in Dr. Plummer's paper, I find that the exophthalmic poison will always be exaggerated by the simultaneous presence of any other poison such as worry, overwork, alcohol, or nicotine, and this exaggeration always appears wherever the manifestations of Graves' disease are most marked, varying in different individuals.

Dr. R. C. Cabot. I would like to ask Dr. Wilson if he finds his work in opposition to Marine's work in Crile's clinic or in confirmation of it?

Dr. Wilson: I wish to call attention again to two types of thyroid glands, viz., those that are hyperplastic and toxic, and those that are regressive and non-toxic. Extracts of glands of these two types act differently when inoculated. As to Dr. Billings' remarks on dilatation of vessels; we find that the vessel walls are thickened rather uniformly in toxic goitre cases.

In reply to Dr. Cabot's question, I would say that the points of difference between my work and that of Marine are due to differences in clinical classification of cases. We have been able to take Dr. Marine's specimens and tell him what were the clinical manifestations in the cases with a considerable degree of accuracy.

Dr. Plummer: I would like to add somewhat to Dr. Wilson's reply to Dr. Cabot. In 1908, Dr. Wilson pointed out that in 80 per cent. of

the cases clinically called exophthalmic goitre, there could be demonstrated hyperplasia of the thyroid gland, and that the remaining 20 per cent. of the cases were not in fact exophthalmic goitre. The point of the present paper is that in cases showing evidence of intoxication there is always hyperplasia of the thyroid. Not all cases are intoxicated and in such the gland will show regressive changes.

Dr. Blackford: The extracts of definite exophthalmic thyroid produce drops in the blood pressure of dogs three times greater than the depression caused by other extracts.

Dr. Vaughan very truly said that all foreign proteins are poisons to dogs, and egg white, horse-serum, and other proteins have been used by us in our experiments, but the behavior of the blood pressure after the injection of these substances is entirely different from that observed after injection of thyroid extracts.

We have not been able to work out the physiologic mechanism of the drop in blood pressure, and we have not used barium chloride or nicotine in our work.

REPORT OF STUDIES ON PNEUMONIA

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Our problem has been a clinical one, a search for methods of improving the therapy of the most formidable enemy with which we, as physicians, have to deal. At the outset, however, we have recognized the futility of attempting the immediate employment of every measure that might be empirically recommended. The method which has seemed more logical and the one we have pursued has been to try to learn more of the fundamental nature of the disease in order that, with further knowledge, methods of combating the various factors concerned might be made evident. It is needless to remark that the various steps in the process are almost as obscure as they are in tuberculosis. To the student of infectious disease the last word has not been spoken when the etiological agent is named and the clinical complex described; even the discovery of a cure will not necessarily complete the study.

As to why pneumonia arises, we have many theories but little evidence, though our conceptions have been much clarified during the past few years. How does the growth of pneumococci within the body give rise to the local reaction on the part of the tissues, and especially to those general reactions which constitute the disease? This latter problem is of most importance to the physician whose aim is to cure disease, since its solution is of prime importance for therapy. The idea that bacteria act mechanically in causing disease had long ago to be given up. The only conception which

at the present time it seems possible to offer direct evidence for or against, is that chemical substances play the intermediary role between the bacteria and the host. The demonstration of such chemical substances is lacking. Our search for light on this step of the process has taken two directions, since it is possible that true specific toxins may be concerned or, on the other hand, that the effects may be due to simple non-specific, possibly inorganic substances arising during the metabolic activities of the bacteria. Pneumococci produce acids in culture media. It is not inconceivable that they produce acid in the body. Metabolic studies in pneumonia carried on by Dr. Peabody, while of great interest, have not yet afforded evidence that the intoxication is the expression of such simple activities on the part of the bacteria. The demonstration by Drs. Peabody and Butterfield that in certain cases methemoglobin is produced in the body as a result of the activity of pneumococci, explains why in such cases the oxygen-carrying capacity of the blood is lowered. Their studies show, however, that this cannot be simply a result of acid production, but is likely the effect of a more complex poison.

The search for soluble poisons in the cultures of pneumococci has not been fruitful. More promising have been the results of efforts to obtain such poisons from the bodies of the bacteria. We need only to refer to the production of the so-called anaphylatoxin by Friedburger, toxic split products by Vaughan, and toxic autolysats by Rosenow. In all of these cases, the conception of the investigators is that as a result of ferment action, either by the ferments of the body or the ferments of the bacteria themselves, digestion of the bacterial protein occurs and the products of such digestion in some stage of the process are toxic. However, this theory, attractive as it is and supported as it is by the apparent demonstration by Abderhalden of the increased development of ferments in the infected body, must receive general application to the nature of infection only with caution. Through the interest aroused by this conception, attention has been drawn away from an older view which was first propounded by Pfeiffer, who brought forward some evidence to substantiate it, namely, that the constituents of the bacterial bodies might have a primary toxicity.

In a discussion before this society last year, it was mentioned that it had found that if penumococci were dissolved in dilute solutions of bile, the resulting solution was highly toxic when injected intravenously into guinea-pigs and rabbits. In this instance the bodies may go into solution within two or three minutes, so that there is little likelihood that digestion, as ordinarily understood, can have occurred. We must suppose that the toxic substances exist preformed within the bacterial cells. Toxic substances having similar action may also be obtained from pathological exudates in which bacteria may have dissolved.

During the present year considerable further study has been made of this toxic solution. It is thermolabile, is destroyed by heating one-half hour at 55°, it deteriorates very rapidly even on ice, it may be dried in a vacuum, retaining its toxic properties, however, it is readily absorbed by various absorbents, and so is thrown out of solution by colloidal iron and it does not pass through a Berkefeld filter. So far no non-toxic substances have been found to neutralize it. It is hemolytic, even when considerably diluted. This latter property of the solution seems to be dependent on the same substance on which the toxic effects in the animal depend, at least, both properties are altered by the same agents. The discovery of this hemolytic property has greatly facilitated the study of this substance. Lastly and most important, it has been possible to demonstrate that the serum of immunized animals is able to neutralize both the hemolytic and general toxic effects of the poison. These immune substances are present in the serum of animals immunized by injection of living bacteria, and to a less degree in the serum of those injected with the bile extract alone. This demonstration of the production of immune substances renders justifiable the conclusion that we are dealing with a true toxin in the Ehrlich sense. While it would seem possible that a step has been made toward the solution of the problem concerning the relation of the bacteria to the symptoms, we would be far from asserting that the pneumococcus toxin has been discovered.

The final step in the pneumonia process relates to recovery and cure. The facts that spontaneous recovery occurs, and that animals may readily be made resistant to infection by a process of immuni-

zation, give definite proof that the body contains within itself the mechanism for overcoming infection. The exact nature of this mechanism, however, is still in doubt. One thing is certain, however, and that is that substances preventing the development of infection are present in the sera of patients following recovery and in the sera of immunized animals. The proof that these substances in the sera are responsible for spontaneous recovery, or have a curative value in the infected animal, is more difficult to adduce. It has been claimed by Neufeld and others that mild infections in guinea-pigs and other animals may be cured by the injection of such immune sera, even some hours after the infection has started. It must be admitted, however, that usually the injection of immune sera into susceptible animals, even only a few hours after infection with virulent organisms, seems to have little or no effect in stopping the progress of the disease. Man, however, as compared to the laboratory animals, is relatively highly resistant to pneumococcus infection and the process tends to remain localized. It would theoretically seem not impossible, therefore, that if the infected man could be supplied with a sufficient number of such immune bodies, he might be aided in overcoming infection. Such immune sera have been tried, and the results have been reported before this society.

The results heretofore obtained were not sufficiently promising to cause the method to receive any wide application. Lately, however, an immune serum of quite high potency has been produced by Neufeld. His studies led him to the conclusion that such antibacterial sera in neutralizing action do not follow the law of multiple proportions, but that the action of such sera is dependent on the concentration of immune bodies in the medium, and this is to a considerable extent independent of the degree of infection. In other words, in the body after the immune bodies are distributed, they must still be present in a certain concentration in order to be active, which he calls the "schwellen wert," or threshold concentration. If a mouse weighing 15 gms. requires 0.05 c.c. serum to overcome even a mild infection, a man weighing 75 kgms. would require a proportionate amount, in the present case 250 c.c. Experimental studies by Dochez do not permit entire agree-

ment with Neufeld as to his interpretation, yet we agree with his main conclusion that it is probable that one reason why such sera have not been more efficacious is that they have not been employed in sufficiently large amounts. The intravenous administration of large amounts of the Neufeld serum and of the Römer serum have been made by Géronne, Weitz, and by Beltz. In certain of the cases the effect of the administration of such serum has seemed too favorable. Neufeld, however, in studying the effect of his serum experimentally, found that his serum was ineffective in protecting animals against certain other strains of pneumococci than those used for immunization. He, therefore, emphasized the necessity of rendering such sera polyvalent.

About two years ago, we commenced the immunization of a horse with a strain of pneumococcus obtained from Neufeld. This was the same strain used by him in producing his immune serum, which serum he had shown to be effective against a considerable number of races of pneumococcci studied by him. This horse yielded a serum which in animal experiments was very efficacious; in mice 0.2 c.c. was able to protect against 0.5 c.c. of culture, of which one ten-millionth killed. During the winter of 1911–12, twenty-three strains of pneumococci were isolated from pneumonia patients, mostly from the blood. Experiments on animals showed that the serum was protective against twelve of these. Against the remaining eleven it had no effect. By immunizing rabbits against these remaining strains and studying the cross-protection of the sera obtained, it was found that five of the strains fell into the same group, that is, a serum produced from one of them protected against the other five. This serum afforded no protection, however, against organisms of the Neufeld type. Two of the organisms were of the Pn. mucosus type, and the remainder showed no interrelationships. It therefore seemed that the pneumococci obtained from pneumonia patients could be tentatively divided into four types: (1) a type like the Neufeld strain which we have called Type I, (2) a type like the five strains I have mentioned, which we have called Type II, (3) Type III, the so-called Pn. mucosus, (4) Type IV, or better Group IV, in which are placed those pneumococci which do not belong to any of the above types and the

individual members of which so far do not seem to show any immune relationships. We then proceeded to immunize a second horse to a pneumococcus of Type II.

During the present winter pneumococci from fifty-two cases of pneumonia have been carefully studied. Of these, twenty-three belong in Group I, six in Group II, eight in Group III and fifteen in Group IV. In addition, ten other cases of pneumonia due to the pneumococcus were treated. In these the organisms were not classified in some because the cultures were lost; in others we still have the organisms but classification has not yet been made. So it is evident that a considerable group of cases are due to pneumococci against which neither Serum I nor Serum II is efficacious. It has become evident, however, that pneumonia due to Types I, II, and III is much more serious than that due to Type IV. Of eight cases in 1911-12 due to Pn. I, four died and four recovered. Of five cases due to Type II, all died, and of two due to Pn. mucosus, both died. The reason why during that year such a large proportion of cases were found to be due to Types I and II was that the study was almost entirely made of organisms isolated from the blood. Types I, II, and III induce the most severe types of pneumonia and are much more likely to invade the blood than Type IV. That the pneumonia due to Type IV is not so serious is shown by the fact that of the fifteen cases during the present winter due to this type, all recovered.

It has therefore become evident from our study that the problem in pneumonia consists in the specific treatment of cases due to organisms of Groups I, II, and III. As I have mentioned, we have obtained a very active horse serum against the organisms of Type I, a second serum somewhat less efficacious against organisms of Type II, but so far it has been entirely impossible to produce an active serum against the third type, Pn. mucosus, though attempts are still in progress.

Our bacteriological studies have therefore brought evidence for a second possibility why the administration of immune serum in pneumonia has not been efficacious. The administration to a patient with pneumonia of serum which is entirely without effect on the organism concerned may not only have no favorable action,

but it is possible that the result may even be unfavorable. Some years ago I called attention to this pro-infective action of normal foreign serum. In order to administer immune serum rationally, therefore, it becomes necessary that we have a method for detecting accurately and quickly the nature of the infecting organism. We have been aided in developing such a method by the fact that the agglutinating reactions of these organisms seem to be absolutely specific. Organisms of Type I are agglutinated by Serum I, but not by Serum II, even when employed full strength, and a similar reaction is present with Type II and Serum II. The problem therefore becomes one of rapid isolation of the organisms from the patient. At present, when a patient with pneumonia is admitted to the hospital, a culture is immediately made from the blood and also one from a portion of sputum coughed up from the lung, or when this is not obtainable, a culture is made directly from the lung by the insertion of a needle. This seems to be without danger. Where there are quite large numbers of organisms in the sputum, if these are virulent, a culture may be most rapidly obtained by injecting the sputum into the abdominal cavity of a mouse. After four or five hours the peritoneal cavity may be washed out with salt solution, the cells thrown down in the centrifuge and one so obtains a suspension of the organisms. However the culture is obtained, the aggultination test is at once applied. If the organisms fails to agglutinate with either Serum I or II, it is, of course, useless to undertake serum treatment. If, however, one of the sera agglutinates the organism, treatment may be commenced at once with the appropriate serum. Later the organisms have been studied by testing the protective power of the serum, and in all cases the protection test has corresponded with the agglutination test.

So far not a large number of cases suitable for treatment have come under our observation. In all, serum has been administered in seventeen cases, but in one of these, one of the first, a further study of the organism showed that it was of Type IV, so the administration of serum was discontinued. In two cases the patients were brought in in the last stages and died a few hours after the administration of the serum. Of the fourteen cases which we have

really treated, therefore, eleven were of Types I and three of Type II.

The method of administration of the serum was as follows: on admission 2 c.c. of serum were injected subcutaneously to discover if the patient was hypersensitive. As soon as the type of organism was determined, 50 to 100 c.c. of the serum, diluted 50 per cent. with salt solution, were injected intravenously. We were guided in the following treatment by the condition of the patient. Usually the serum was not administered oftener than every twelve hours. The treated patients received totals of from 190 to 460 c.c. of serum, except one who received a total of 770 c.c. serum. Treatment was commenced on the second day in one case, on the third day in four cases, fourth day in three cases, fifth day in three cases, and sixth day in three cases.

The patients treated were all seriously ill, the most severe cases we have had during the winter. Of the eleven cases due to Pn. I, all recovered but one, and of the three cases due to Type II, one died. This patient, however, objected to the treatment and would not allow its continuation, so it was not thoroughly done. When we consider that the mortality is chiefly among the cases due to Types I and II, the result is certainly not discouraging. The number of cases is much too small, however, for any conclusions whatever to be drawn from the results as regards mortality. Our total mortality during the winter among sixty-seven cases, treated and untreated, has been but (eleven) 16 per cent. while last year it was 47 per cent. I am informed, however, that the mortality in other hospitals in New York has also been lower. It will be interesting later to find whether or not the lowered mortality in certain years is due to the greater prevalence of pneumonia due to organisms of Type IV.

In the one fatal case among those well treated, the serum had no demonstrable effect so far as the patient's condition was concerned. The treatment was commenced on the fifth day and he had a total of 350 c.c. of serum. The serum had no effect on temperature; we might apparently just as well have injected salt solution. Yet the organism obtained from the blood was a typical I. Why there was this entire lack of reaction on the part of the

patient, it is impossible to say. In the other patients the effect of the serum was unmistakable. In eight cases pneumococci were isolated from the blood before the treatment was commenced. In all cases blood cultures were made before each treatment, and in all of these eight cases after one treatment and before the second (or within eight to twelve hours) the blood had become sterile. The conclusion, therefore, seems justified that the serum sterilizes the blood and prevents the invasion or growth of pneumococci in it. In a number of cases, estimation of the protective substances in the blood following the injection has been made, and it has been possible to demonstrate such protective substances following an injection, while, as the previous studies of Dochez have shown, these only appear in untreated cases about the time of crisis.

In all cases there has been a temperature reaction following the injection. The temperature usually rises, then falls, but does not remain low. In two instances the rise of temperature has been marked. One case had a temperature before injection of 106.2°. The patient was in a very serious condition. Following the injection thirty-five minutes, the temperature rose to 109.2° and then fell. The patient's condition was so serious that in spite of the severe reaction, a second injection was given six hours later, when the temperature was 103.5°. Following this the temperature fell to 97.5°. In twelve hours there was a fall of temperature of 11.7°. This patient has recovered. In another patient the temperature rose from 105.8° to 107.2°. This patient also recovered. In the other cases the rise of temperature following the injection was only one or two degrees. I have purposely avoided exhibiting temperature charts, as unless all were shown, they might be quite misleading.

All the patients treated felt better following the injection of the serum, and this seemed more than a mere psychic effect. In many of the cases there was a very manifest lessening of the intoxication. This is of special interest, since we have demonstrated that the serum has a definite antitoxic action on the toxin which we have been studying.

In no case was one injection of serum sufficient to bring on

crisis. The best results were certainly obtained where the serum was administered early. In the early cases, even though pneumococci were present in the blood, the lung lesion did not extend. On the whole, however, there was no special tendency for the lung lesion to resolve rapidly. If anything, the opposite seemed to be the case, and this has been noted by others who have administered serum. One of the patients developed a pneumothorax with empyema, which was operated upon. Recovery followed. Fortunately in this case lung puncture was not done. Several of the cases developed signs of fluid, but the fluid was sterile and disappeared without operation.

Most of the cases showed urticaria at various periods following the injection, and in three there occurred quite severe serum disease, with painful joints, at periods of from seven to twelve days following the treatment. While this is unpleasant, it does not seem that it is worth considering when the treatment of so serious a disease as pneumonia is under consideration, especially since von Pirquet has never seen a fatal case.

It should be asked why should not a polyvalent serum be employed, immunizing with one of each group. This may later be possible, but it is first of importance to make certain that a univalent serum is useful, and this can only be done in the manner described.

We have, therefore, shown that the pneumococci causing pneumonia are of several types, each from an immunological standpoint absolutely distinct. Immune sera to two of these types have been produced. Treatment of suitable patients with the proper serum seems to give results which are promising, certainly not discouraging. A method of obtaining a toxin has been devised and the immune serum has been shown experimentally to have a distinct antitoxic action. The demonstration of a cure for pneumonia has not been made, but we hope that a line of attack has been developed which may be of value in lessening the mortality from this serious disease.

DISCUSSION

Dr. V. C. Vaughan: I can but express the appreciation which a paper such as that presented by Dr. Cole deserves. The readiness with which the pneumococcus breaks up with the liberation of a poisonous substance was shown by Dr. Cole's work. We have in our laboratory some pneumococcus germ substance, in the form of a pearly white powder, which has been kept for seven years. Seven years ago it killed guinea-pigs in a dilution of 1 in 40,000; and now it kills in a dilution of 1 in 40,000.

The poison is probably liberated through the agency of an intracellular ferment.

Dr. C. S. Bond: What were the ages of the patients reported as successfully treated?

Dr. Cole: One patient was a boy, aged twelve years; the others were adults between twenty and sixty years of age.

UROBILIN:[1] ITS CLINICAL SIGNIFICANCE

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1. Introduction 617
2. Summary of Quantitative Methods for Urobilin Estimation . . 621
3. Discussion of Methods 625
4. Methods 634
5. The Excretion of Urobilin in Urine 637
6. The Excretion of Urobilin in the Stools 643
7. The Excretion of Urobilin in Bile 646
8. Urobilin in the Blood 648
9. Animal Experiments 652
10. Clinical Reports 659
11. Miscellaneous Cases 671
12. Conclusions 672
13. Bibliography 677

1. INTRODUCTION

The numerous studies made upon urobilin and urobilinogen during the forty-four years since its discovery by Jaffe while adding much to our knowledge of its chemistry and its clinical occurrence still leave much to be desired as to methods for its estimation and as to its clinical significance. Some investigators are inclined to look upon it from the standpoint of hemoglobin metabolism, while others consider it only in reference to hepatic insufficiency. Its relationship to the presence or absence of bile in the intestine

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has been a subject of considerable dispute, but in the main the contention of Friederich von Müller that it can originate only from the bacterial decomposition of bile reaching the intestine is accepted. Nevertheless the assertion of Fischler that it can originate in the liver itself seems to us probable. Whether it is then formed within the liver cell or is produced by decomposition of bilirubin in the biliary passages it is impossible to state. A wide variability in point of view is reflected throughout the available literature. It has been our intention in entering upon a study of this substance to endeavor to estimate its present value as an aid in diagnosis and prognosis and we must frankly admit that it has been disappointing in some particulars perhaps largely due to the imperfections of the present methods of its estimation and to its evident instability. Besides when such variable factors as the bacterial fermentations within the gut, the absorption from it, the activity of the liver, the elimination of bile, the eliminative power of the kidney, the rate of destruction of the red-blood corpuscles, the activity of the spleen, etc., have to be taken into account, it is not surprising that difficulty should arise in interpreting findings and in correlating the diverse views of many investigators and clinicians.

The interesting spectroscopic, fluorescent, and color tests for urobilin and its mother substance urobilinogen and their common occurrence in the body excretions, especially in disease, naturally stimulated much research as to their composition and origin and many clinical observations as to their significance. The Ehrlich aldehyde test shown by Neubauer to be due to urobilinogen received particular attention. The method of estimation with Citron's or other simple spectroscope of the urobilin and urobilinogen together proved with us to be fairly simple and to lend itself readily to approximate quantitative studies based on the disappearance of the characteristic absorption bands between D and E and B and F with successive dilutions.

The term "urobilin" is not applied to a single body but to a group of derivatives of blood and bile pigments containing the pyrrol nucleus.[1] Throughout our work we have considered urobilin

[1] See preliminary communication, Jour. Am. Med. Assoc., 1912, ix, 929–933.

and its mother substance urobilinogen as practically the same, and have endeavored always to estimate them together in making clinical and experimental observations. The confusion between the two and the lack of a generally accepted theory of the origin of these substances is the cause of the present striking lack of uniformity in the interpretation of clinical and laboratory results.

The most prominent of these theories are the hematogenous, the hepatogenous, the nephrogenous, the histogenic and the enterogenous. The latter is undoubtedly the most satisfactory, although it does not fully explain the origin of all urobilin within the body, for instance, that of some hepatic disorders (Fischler) and some cases of blood destruction and extravasation. In brief these theories are as follows:

Hematogenous Theory. This theory is that the urobilin can be but is not necessarily derived from blood pigment. It is based upon the somewhat uncertain evidence of the long known occurrence of urobilinuria in hemorrhage of the brain (von Bergmann), in blood extravasations (Kunkel), in extra-uterine pregnancy (Dick), in hemorrhagic ascites (such as the famous case of Gerhardt in which there was also a carcinomatous closure of the ductus choledochus); after hemolytic processes, in sulphonal poisoning, in paroxysmal hemoglobinuria, and in scurvy. While it is true that there is the possibility in many of these reported clinical observations of existence of definite hepatic disturbance, still there is enough experimental evidence to warrant the assertion that at times urobilin can be derived directly from blood pigment without the intervention of either the liver or the intestine.

Hepatogenous Theory. The principal tenet of this unsatisfactory theory is that there is failure on the part of the liver in its normal decomposition of hemoglobin and that as a result of this insufficiency urobilin is formed and reaches the kidney through the blood stream and is there eliminated, or is added to the intestinal contents by the bile. A somewhat strict interpretation of this theory is that there is a direct formation of urobilin within the liver cell or at least within the bile passages from the bile pigment.

Nephrogenous Theory. In brief this is based upon the fact that urobilin as such is very rarely found in the blood and that

it reaches the kidney in the form of bilirubin which is reduced to urobilinogen in its passage through the renal epithelium. Herscher states that kidney substance can reduce bilirubin, but surviving kidneys with bilirubin circulating in their blood secrete no urobilinogen but only bilirubin in the collected urine. The principal argument against this theory is that urobilin does not occur in many cases of jaundice.

Histogenic Theory. This theory that hemoglobin or bile pigments are reduced in the tissues to urobilin, then reabsorbed and eliminated, offers an insufficient explanation of the various known phenomena.

Enterogenous Theory (Friederich von Müller). While not meeting all conditions this theory is based on the explanation of the established facts of urobilin formation. In brief it is based on the finding that bile pigment reaching the intestinal lumen undergoes a change into urobilinogen and urobilin caused by bacterial decomposition. It may then be absorbed into the capillaries of the portal system and so reach the liver parenchyma. If the liver is normal the major portion of the urobilin is destroyed or synthetized to bile or blood pigment. A portion may be secreted in the bile and so be returned to the intestinal lumen to be reabsorbed or passed off with the stool. When the liver parenchyma is damaged these changes in the urobilin may not take place but it passes on into the general circulation. It reaches the kidney through the blood and is eliminated in the urine. This theory is principally sustained by the absence of urobilin in the urine in any quantity in cases of obstruction of the common duct. We will not stop for a complete discussion of these theories since view-points vary and there is no common agreement at the present time. We can safely assume that, as a rule, the presence of urobilinuria is indicative of the fact that bile is reaching the intestine, and that large amounts of urobilin in the urine usually mean that there has been either abnormal destruction of red-blood corpuscles, or an insufficiency of the liver to perform its normal functions. A large amount of urobilin in the stool indicates increased blood destruction. Urobilinuria frequently disappears in severe diarrhea. Although urobilin is normally present in the urine in small quantities, its presence cannot

be ascertained by the ordinary qualitative tests—a positive reaction with Schlesinger's zinc acetate test or Ehrlich's aldehyde test is not found in normal urine. It is increased in many pathological conditions. It is commonly increased in infectious diseases, in diseases where there is widespread hemorrhage, traumatic or otherwise, in pernicious anemia, malaria, cardiac decompensation, various forms of liver and gall-passage disease, and in numerous intoxications such as those due to alcohol, chloroform, lead, and carbon monoxide.

2. SUMMARY OF QUANTITATIVE METHODS FOR UROBILIN ESTIMATION

The following tabulation gives only the most essential points of the methods which have been used.

The Urine. Almost all the work done has been with the urine. As regards the urine the methods may be roughly devided into (1) those requiring a separation of the urobilin from the urine by means of precipitation with ammonium sulphate; (2) those depending on the spectroscopic absorption bands of urobilin; (3) those based on the property of fluorescence; and (4) colorometric methods depending on the violet color produced by copper sulphate in urobilin solutions.

1. *Methods Involving Salting out of Urobilin by Means of Ammonium sulphate.* Hoppe-Seyler in 1891 estimated urobilin in urine gravimetrically. The acidified urine was saturated with ammonium sulphate, the precipitate extracted with chloroform and alcohol. The solution was evaporated; the residue dissolved in ether, filtered, evaporated, the residue dissolved in alcohol, evaporated and weighed.

Viglezic in the same year recommended a method which depended on the salting out of the urobilin with ammonium sulphate and its solution in alcohol. The amount was gauged by noting how much of this solution was required to produce a certain grade of fluorescence or the appearance of the spectroscopic absorption bands, when it was added to a solution of zinc chloride.

Studenski added copper sulphate to the urine, precipitated with ammonium sulphate and dissolved the copper compound of urobilin in chloroform. This color was compared with that produced by copper sulphate in a solution of urobilin of known strength.

Ladage recognized the necessity of taking the urobilinogen into account and recommended that iodine should be added to convert it to urobilin. The urobilin was then precipitated by saturation of the urine with ammonium sulphate, and the acid chloroform solution diluted until the spectroscopic absorption became invisible. In Friederich von Müller and Huppert's method a mixture of barium chloride and barium hydrate is added to the urine, the precipitate is filtered off and washed with hot water. The excess of barium in the filtrate is removed by sodium sulphate, and the filtrate after neutralization with sulphuric acid is saturated with ammonium sulphate. The precipitated urobilin is filtered off, allowed to dry in the air and extracted three times after acidification with a warm mixture of alcohol and ether. This solution is then evaporated to a convenient bulk and the amount of urobilin estimated spectrophotometrically.

Charnas in 1909 gave us an alternative method to one based on the spectroscopic characteristics of urobilin, a gravimetric method in which after all urobilinogen in an ether extract of the urine has been converted into urobilin by exposure to sunlight, the urobilin is separated by water from the ether, and after filtration precipitated by ammonium sulphate, dried, dissolved in alcohol, the alcohol evaporated in vacuo and the residue weighed.

2. *Spectroscopic Methods.* Gerhardt (1889) and Beck (1895) made estimations by means of the spectrophotometer using Vierodt's tables of the grade of light extinction in different regions of the spectroscope in normal urine and solutions of urobilin.

Saillet (1897) extracted the freshly passed urine with acetic ether. In another specimen the urobilinogen was converted into urobilin by exposure to light and then extracted. The two extracts are added together and diluted until the spectroscopic band disappears.

Conner and Roper (1908) made approximate measurements of the

amount of urobilin in urine by noting the number of dilutions required to obliterate the urobilin band in the urine. They recommend the addition of a few drops of Lugol's solution to the urine in order to convert the urobilinogen into urobilin.

Auché (1909) found that a solution of urobilin of 1 in 200,000 dilution prepared by a method he describes is sufficient to make the five absorption bands of potassium permanganate all of equal intensity, although without it some are lighter than others. He therefore superimposes the urine, which in some cases has to be extracted with a thymol chloroform solution, over a solution of potassium permanganate, and dilutes the urine or its extract until all the bands are of equal intensity.

Simpson (1910) acidifies the urine with sulphuric acid and exposes it to light for some time in order to convert urobilinogen to urobilin. It is then diluted until the urobilin band disappears. This method gives fairly accurate results when a dilution of 15 or more volumes were necessary. With smaller amounts the reading was apt to be obscured by other pigments.

Hausmann (1913) adds copper sulphate to the urine and dilutes until the spectrum becomes invisible.

Henocque, Hayem, Gautretet, Deniques, Riva and Zoja have used one modification or another of these spectroscopic methods.

Charnas (1909) makes the urine alkaline, allows it to ferment at 37° C. for twenty-four to forty-eight hours, acidifies with tartaric acid, extracts with ether, and petrol ether. To a portion of the ether extract an ethereal solution of paradimethylamidobenzaldehyde is added and two or three drops of absolute alcohol saturated with hydrochloric acid gas. After dilution if necessary with alcohol a spectrophotometric reading is made.

3. *Methods Depending on the Property of Fluorescence.* Grunin (1893), Fischler (1906), Grigant and Monod (1909), Hildebrandt (1909), and Descomps (1909) gauge the amount of urobilin by the intensity of the fluorescence present in the zinc salt filtrate of the urine. Various devices are adopted to aid the conversion of urobilinogen into urobilin.

4. *Colorometric Methods.* Bogormaloff (1882) used a colorometric method, depending on the depth of the red-violet color

produced in a chloroform extract of urine containing urobilin by the addition of copper sulphate.

Braunstein (1903) used a modification of this method.

Flatow and Brunell (1913) estimate the amount of urobilinogen in fresh urine from the depth of the red color given on the addition of Ehrlich's reagent. As a standard they use a phenolphthalein solution to which a few particles of metallic sodium has been added.

Brugsch and Retzlaff (1912) modify Charnas' method by extracting the alkaline urine first with ligroin. They make the final reading with Plesch's colorimeter, using a solution of Bordeaux red as the standard.

The Stools. Quantitative estimates of urobilin in the stools have been carried out by comparatively few investigators. Gerhardt at first used a somewhat complicated process of extraction and purification, but later, except in special cases, simply extracted with acid alcohol and read spectrophotometrically. Auché extracts with alcohol, removes other pigments by shaking with ligroin, and thereafter makes the same spectroscopic determination as he employs in urine extracts.

Simpson (1910) mixes the day's feces with water and adds enough dilute sulphuric acid to make the mixture distinctly acid. For one or two days full exposure to light was allowed to convert the chromogen into urobilin. Filtration is then carried out and the residue repeatedly extracted until the filtrate becomes colorless. Direct examination of the filtrates is made and the amount determined from the degree of dilution required to obliterate the spectroscopic band.

Brugsch and Retzlaff (1912) attempt to convert all the urobilin into urobilinogen by allowing the stools to stand for some time before extracting with ligroin to remove indol derivatives and then with acetic ether. After the addition of paradimethylamidobenzaldehyde they make a colorimetric determination as in their method with urine.

Serum. No quantitative work has been done with serum. The methods employed for the detection of urobilin in serum were reviewed by Conner and Roper. We shall refer therefore only to those which have appeared since their publication.

Morel and Monod (1908) add alcohol to the serum and heat to boiling for half an hour. The filtrate is concentrated and a drop of Obermeyer's reagent and an alcoholic solution of zinc acetate and acetic acid added. After twenty-four hours the filtrate is examined for fluorescence.

Auché (1909) adds a solution of iodine in potassium iodide to the serum and afterward some cyanate of zinc in ammonia and filters. The filtrate is examined spectroscopically.

Fromholdt and Nersessoff (1912) precipitate the oxalated plasma with alcohol, filter, concentrate, acidify, shake with amyl alcohol, and then with alkaline water. The water is then made acid and shaken with amyl alcohol and examined spectroscopically.

3. DISCUSSION OF METHODS

In reviewing the literature on these methods it was evident that the one main difficulty encountered by all investigators was the problem of separating urobilin and urobilinogen from the other coloring matter present in the excretions without, at the same time, destroying more or less of it. Many had frankly given up the attempt to attain any but the roughest purification and had relied on the intensity of the physical properties of fluorescence or of light absorption. In doing so they had of course confessed that their results were not quantitatively accurate, for variations in the impurities present would undoubtedly affect the basis on which their determinations rested. Others have not remained satisfied with this but have attempted to attain at any rate approximately pure solutions before estimation.

The question as to which of these two methods produced the better result depended on whether more was gained in accuracy than was lost by destruction of urobilin in the various precipitations, separations, and evaporations required.

It appeared to us that there was one way in which the question could be answered. When undiluted urine is examined spectroscopically nothing is seen as a rule except a general absorption of light which becomes deeper and deeper toward the blue end of the

spectrum. Even if urobilin is present the absorption band cannot be clearly differentiated. When the amount of urobilin, however, is much larger than the other light-absorbing substances present, one finds that on simple dilution with water the band between B and F becomes more and more distinct so that it at last stands out sharply. On still further dilution it begins to fade, and a more or less definite point is reached at which it becomes invisible, when the full amount of light is allowed to pass through the spectroscope, but can still just be seen when the light is diminished. In some urines one may have to carry the dilution to eighty or more times the original volume of urine to reach this point. At this dilution the disturbing effect of other substance is negligible. Such urines afford an excellent means of deciding as to whether any particular manipulation leads to a loss of urobilin or not, because the number of dilutions required to remove the urobilin band before and after the procedure can be very readily determined. We were fortunate at this time in having under observation for several months a case of bronzed diabetes in whose urine unusually large amounts or urobilinogen and urobilin were constantly present.

Practical experience with this and other methods very quickly showed us that any and every tried means which may be applied to separate urobilin from the urine was associated with more or less loss. Extracts from precipitations with ammonium sulphate, separations by ether, chloroform or thymol chloroform solutions, and processes of evaporation, with or without heat, all led to a greater or less diminution of the spectroscopic dilution value. Such methods are applicable in the endeavor to obtain pure urobilin, but it seems to us that they can have no place in any quantitative estimation, for the amount destroyed is too variable and too incapable of control. The one salient fact which has to be kept constantly in mind in choosing a method of estimation is that almost any manipulation is apt to be associated with more or less loss of urobilin. It is better to recognize from the first that ordinary chemical methods are not applicable to a substance which is so labile, and that their employment gives only a fallacious appearance of accuracy. Any gravimetric method for this reason seems to us to be entirely out of question. Solutions of urobilin or urobilinogen

may no doubt be obtained in a state of sufficient purity to admit of spectrophotometric determination, but with the means which have hitherto been employed for this purpose the error by loss so far outweighs any increase of accuracy in the final determination as to make results obtained by such methods of very doubtful value. Yet in the case of all urines where the amount of urobilin was not exceptionally large and in dealing with stools some preparation was necessary, for no direct reading could be made. After trying a large number of procedures the conclusion was reached that the most innocuous of all was to mix equal parts of urine and a saturated solution of zinc acetate in alcohol and after mixing and shaking to filter. This is Schlesinger's qualitative test for urobilin. A small amount of urobilin may be absorbed by the precipitate, and at first we filtered under pressure and washed the precipitate with alcohol, but laterly we found that the error was so small compared with other unavoidable sources of error, that in routine clinical examinations we have simply taken the first fraction of the filtrate.

Another necessary procedure also soon became apparent. It has of course long been known that on adding acid to a urobilin solution the position of the absorption band is altered, but we had not gathered that the intensity was changed to the extent which we found in many urines. Sometimes the increase in the number of dilutions required to obliterate the band was ten times as great in filtrates which had been made strongly acid as in the fresh filtrate. It was obvious that unless constancy could be attained in this point, no results of any value could be obtained. The intensity of the spectroscopic characteristics of urobilin are as dependent on reaction as is the property of fluorescence. The difference is that to attain maximum fluorescence a nice balancing of reaction is required, whereas the strongest absorption band is obtained in a strongly acid solution and an excess of acid does no harm. All that is required therefore is to be sure that enough acid is present. For this reason alone the spectroscopic methods are to be preferred to those based on fluorescence in which large errors may arise from slight variations in reaction.

Still another essential point in any method is that the uro-

bilinogen as well as the urobilin shall be taken into account, and that if possible the quantitative relationship between the two bodies shall be established so that the result can be expressed as a single figure. Urobilin is simply an oxidation product of urobilinogen; from the clinical or physiological points of view they have exactly the same significance. Urobilinogen is potential urobilin. In any specimen of urine or stool the relative amounts of the two are constantly changing, the amount of urobilin increasing and urobilinogen decreasing the longer the exposure to light and air. In some methods this difficulty is met by keeping the extract for twenty-four hours exposed to light, and it is assumed that all the urobilinogen will then have been converted into urobilin. Others endeavor to hasten the process by the addition of oxidizing agents, and one method takes the opposite course and by alkaline fermentation attempts to convert all the urobilin into urobilinogen. The efficacy of these various procedures was therefore investigated.

The only way by which urobilinogen can be determined except gravimetrically is by the spectroscope through the absorption bands of the pigment produced by its reaction with paradimethylamidobenzaldehyde. We used a solution containing 20 grams in in 300 c.c. of 50 per cent. concentrated hydrochloric acid; 1 c.c. was added to every 10 c.c. of the alcoholic zinc acetate filtrate. This gave a sufficient amount of acid to produce the maximum intensity in the urobilin band and at the same time brought out the urobilinogen spectrum, so that the dilution values of both urobilin and urobilinogen could be read in the same filtrate. The amount of urobilinogen could then be expressed as representing so many dilutions in the same way as with the urobilin.

The first point investigated was the effect of light on urobilinogen. It was found to vary very greatly with the intensity of the light. A few hours' exposure to direct sunlight suffices to cause the complete disappearance of urobilinogen With indirect light the process required a longer time, but after exposure to a diffuse light in a room with ground-glass windows, there was found after twenty-four hours to be an almost complete disappearance of urobilinogen. The following figures show the effect of leaving the zinc acetate filtrates of urine in diffuse room light for twenty-four hours.

UROBILINOGEN

	Filtrate examined at once.	Examined after twenty-four hours in room light.
Specimen 1	32	1
" 2	37	0
" 3	45	2
" 4	25	0
" 5	21	1
" 6	12	0
" 7	7	0
" 8	16	0
" 9	34	0
" 10	40	1
" 11	18	1
" 12	25	0
" 13	19	0
" 14	40	0

The effect on urobilin of a similar exposure to light could not be determined in the same way, since all fresh urine and stools contain urobilinogen which passes over in part at least to urobilin. It was invariably found, however, in these specimens in which by various means the urobilinogen had been removed, that light had a destructive effect on urobilin, as was shown by the diminution in the dilution value after exposure.

Under the influence of light as the urobilinogen diminishes the urobilin increases. The question remained, however, as to how much loss of urobilinogen and urobilin occurred during this process. The precise degree of loss could be found only if we knew the quantitative relationship between urobilinogen and urobilin and the relative light absorbing powers of the urobilinogen and urobilin pigments. These facts are not known, but an indication of the amount of loss of urobilin was gained by comparing the total dilution value obtained by adding together the urobilinogen and urobilin values in the fresh filtrates, in those which had been in darkness for twenty-four hours and in those which had been left in diffuse room light for the same time.

After twenty-four hours in darkness there had been a diminution of urobilinogen from 371 to 301 and an increase of urobilin from 6 to 134. The light-absorbing power of urobilin must then either be greater than that of the urobilinogen pigment, or one molecule of urobilinogen must break up into two or more molecules of uro-

bilin. In any case there is an increase of the total dilution values for urobilinogen and urobilin together, associated with a diminution of urobilinogen and an increase in urobilin.

Fresh urine.		After 24 hours in dark.		After 24 hours in room light.	
Urobilinogen.	Urobilin.	Urobilinogen.	Urobilin.	Urobilinogen.	Urobilin.
32	2	28	11	1	26
37	0	30	12	0	32
45	0	40	12	2	37
25	0	22	8	0	17
21	0	19	14	1	16
12	2	10	7	0	3
7	2	6	3	0	5
16	0	14	7	0	15
34	0	30	12	0	21
40	0	35	13	1	30
18	0	14	10	1	16
25	0	14	9	0	16
19	0	7	4	0	8
40	0	32	12	0	24
371	6	301	134	6	266
Total "Urobilin" 371 + 6 = 377		Total "Urobilin" 301 + 134 = 435		Total "Urobilin" 6 + 266 = 272	

In the filtrates exposed to light there is more than forty times as much urobilin as in the fresh filtrates and twice as much as in those kept in the dark and yet in spite of that the total dilution value is much less, only 266 as compared with 377 and 435. If for a moment it is assumed that the diminution of urobilinogen and increase in urobilin in the filtrates kept in the dark represent the relationship between the two bodies, then 371 − 301 = 70 of urobilinogen should produce 6 − 134 = 128 of urobilin. But the disappearance of 371 − 6 = 365 of urobilinogen in the filtrates exposed to light led to an increase of only 6 − 266 = 260 of urobilin instead of the 667 which should have resulted. It is impossible to explain this decrease in total dilution value except as due to a destruction of part of the urobilinogen or urobilin or both. Since the actual amount of urobilinogen or urobilin destroyed by exposure to light cannot be calculated and varies so greatly with different degrees of intensity of light and with other unknown conditions the conclusion was reached that it was not a means which could be used in any quantitative method to convert

urobilinogen into urobilin, and that as far as possible exposure to light should be avoided in urobilin estimations.

Attention was then turned to the effect of oxidizing agents which have been recommended especially by French investigators. But here also the results were disappointing, for those reagents which were effective in oxidizing the urobilinogen were also very destructive to the urobilin.

Charnas states that if urine is made alkaline and left for twenty-four to forty-eight hours in the incubator all the urobilin will be converted into urobilinogen, which can then be estimated by the spectrophotometer. It is noteworthy that Charnas does not give any estimations indicating the decrease of urobilin and increase of urobilinogen during the process, nor does he bring forward any evidence to show whether or not any part of the urobilinogen or urobilin is destroyed by the fermentation which occurs. It has long been known that in freshly-passed urine urobilinogen is present alone or at any rate in far greater amount than urobilin, suggesting that as it is excreted through the kidneys it is all in the form of urobilinogen and it has been the universal experience that the longer a urine is kept the less urobilinogen will be found in it, so that the statement that in alkaline urine left exposed to the air at a temperature of 37° C. the reverse process occurs and that instead of an oxidation a reduction takes place, is not one which can at once be accepted. We know that in the intestine there is a reduction of urobilin to urobilinogen, but there conditions are present much more favorable to reduction processes than those which are present in urine left exposed to air. Outside the body the formation of urobilin from urobilinogen constantly goes on but to bring about the reverse process the strongest reducing agents we know have to be employed. However, it seemed to us that the question was one which could be decided by the simple spectroscopic method we have outlined.

Readings of the relative amounts of urobilin and urobilinogen in thirty specimens of urine before and after alkaline fermentation at 37° C. were made. In most of the cases fermentation was allowed to continue for twenty-four hours in some for forty-eight hours. The first twelve results are given.

Before fermentation.		After fermentation.	
Urobilinogen.	Urobilin.	Urobilinogen.	Urobilin.
15	5	0	11
12	0	0	9
26	9	7	0
15	5	0	0
12	0	6	0
7	0	8	3
26	9	0	2
19	3	5	2
0	3	0	11
0	5	30	0
17	6	0	1
10	5	50	2

Of these thirty specimens there was a diminution instead of an increase of urobilinogen after fermentation in all except three. In two there was a very considerable increase of urobilinogen, but both these specimens contained some bile, and as we found that urobilinogen was produced in decomposing bile we are inclined to ascribe these exceptions to this cause.

It seemed that these results, so completely at variance with the statement of Charnas as to the effect of alkaline decomposition in urine, might be due to the urobilinogen having become absorbed in the heavy deposit of phosphates in the fermented urines. The experiment was therefore repeated in ten urines, the readings before and after fermentation being made after the specimens which had been made faintly alkaline with ammonium carbonate, had again been made acid with tartaric acid. Before fermentation a total reading of urobilinogen 18 and urobilin 27 was made. After twenty-four hours' fermentation urobilinogen 13 and urobilin 16, and after forty-eight hours urobilinogen 12 and urobilin 4 were recorded. We must conclude then that alkaline fermentation in the dark at a temperature of 37° C. not only does not quantitatively convert urobilin into urobilinogen, but that it has a directly destructive action on both.

Since there was no available way of converting all the urobilinogen into urobilin or *vice versa*, the only alternative was to make estimations of each separately. But could such results be added together and expressed by a single figure? Our knowledge of the chemistry of these bodies is not yet sufficiently advanced to enable us to be sure that one or the other may not be a condensation product

of the other so that one molecule of urobilinogen for instance may break up into two or more molecules of urobilin. No idea as to the relationship between them could be gained by noting the degree of increase in the dilution value of urobilin which followed a decrease in urobilinogen, for the factors concerned are too complex and variable to allow of any true idea being obtained in this way. For while the urobilinogen is being converted into urobilin, both are undergoing other changes and are losing the spectroscopic characteristics on which our determinations rest. In preparations of urobilin and urobilinogen made from bilirubin by Fromholdt's method we found such a lack of relation between the weight of bilirubin and the weight of urobilin produced, and such a variability in the relative amounts of urobilin and urobilinogen formed, that it did not seem likely that in this way either we could successfully determine whether urobilin and urobilinogen were equivalent in value or not. In dealing with two such extremely unstable substances whose presence can only be detected by a single physical property and which are constantly changing into other bodies which we have no means of estimating, the problem of their exact relationship is one whose solution will probably not be definitely established until we have more knowledge of the decomposition products of hemoglobin. For urobilinogen and urobilin are only links in the chain of hemoglobin derivatives, they cannot be regarded as final end-products. However, the problem we were attempting to solve was not the exact quantitative determination of urobilin, but simply the question as to whether any information of clinical value could be gained from urobilin estimations, in spite of the errors necessarily involved in any of the present methods. With this end in view the best that could be done was to add together the dilution values of urobilinogen and urobilin. We do not know that they are equivalent, but on the other hand we know that they are not very different in value. The proportion of the two substances varies so much in different specimens of urine, stool and bile that no comparison can easily be made if the dilution values for each are given separately.

As a result of this preliminary review we determined that the best method would be one which avoided all but absolutely essen-

tial manipulation of the material, one which was based on the most characteristic of the properties of urobilin, the spectroscopic absorption bands, and one in which the attempt to convert all the urobilinogen into urobilin or *vice versa* was abandoned and the results of separate estimations of both were simply added together. When the term urobilin is used without mention of urobilinogen, the sum of the dilution values of urobilinogen and urobilin is intended throughout this paper.

The following are the details of the methods we finally adopted.

4. METHODS

Urine. The method of collection of the twenty-four hours' urine has a considerable effect on the total spectroscopic reading. The vessel in which the urine is collected should be of dark brown glass and should be kept in darkness. Thymol crystals should be added, for even in cases in which no obvious fermentation had occurred we sometimes found a diminution in the total amount if no preservative was present. After measuring the amount of the twenty-four hours' urine, 10 c.c. are mixed with 10 c.c. of a saturated alcoholic solution of zinc acetate, and after a few minutes filtered. If a number of urines are being examined at the same time it is convenient to have test-tubes graduated to 10 c.c. and 20 c.c.; 10 c.c. of the filtrate are taken and 1 c.c. of Ehrlich's solution[1] is added. It was found that this amount produced a sufficient concentration of acid in the mixture to give the maximum intensity of the urobilin band and contained enough of the paradimethylamidobenzaldehyde for the reaction with urobilinogen. The development of the urobilinogen band is not instantaneous. We found that as a rule it had attained its full intensity in a quarter of an hour. The action can be greatly accelerated by heating, but this is to be avoided. It is better to wait for half an hour before making a reading, and during this time the solution should be kept

[1] Paradimethylamidobenzaldehyde . . . . . 20 gm.
Concentrated hydrochloric acid . . . . . 150 c.c.
Water . . . . . 150 c.c.

in the dark. We found that Citron's hand spectroscope[1] was the most convenient instrument to use. The filtrate was washed into a graduate and diluted with tap water until first one and then the other bands of light absorption had disappeared, when the full amount of light entered the spectroscope, but were still visible when the light was partly shut off. This gives a fairly definite end-point, and we did not find any great variation in the readings made by different individuals. It is important of course that the light shall be always of approximately equal intensity. We made the readings in a dark room with a Tungsten electric bulb, holding the spectroscope close to the source of light. In highly colored urines one may be in doubt as to whether or not a trace of urobilin is present, for there may be so much general absorption of light as to obscure the urobilin band in the undilated filtrate. There is no such difficulty with the urobilinogen band which lies between the red and yellow where there is no marked light absorption. With urines containing bile, if the amount of urobilin is not very large, it is necessary to add some Fuller's earth and to have the mixture standing for some time before filtration. If this is done the urobilin band can usually be read even in the undiluted filtrate. The dilution required gives the value for 5 c.c. of urine. If this figure is multiplied by the number of 5 c.c. in the twenty-four hours' urine, the number of dilutions which would have been necessary if all the urobilinogen and urobilin in the twenty-four hours' amount has been concentrated in a volume of 5 c.c. is obtained. For instance, if in a twenty-four hours' urine measuring 1000 c.c. a reading of ten dilutions for urobilinogen and of 20 for urobilin were made, the total urobilin would be $30 \times 200 = 6000$. We tried to determine the dilution value of definite weights of urobilin prepared from bilirubin, but different preparations varied so much in their dilution value that it was obvious that we were not dealing with pure urobilin and we abandoned any attempt to express our results in milligrams of urobilin.

Stools. All the feces passed in the twenty-four hours were collected in the same receiver, the stools being protected from light.

[1] This can be obtained from Paul Altman, Louisenstrasse, Berlin, Germany.

They were then washed into a large graduate and thoroughly ground up with water into a homogeneous paste and water added to $\frac{1}{2}$, 1 or if necessary 2 liters, depending on the quantity of stool. After thorough mixing, 25 c.c. were taken and 75 c.c. of acid alcohol (95 per cent. alcohol, 1600 c.c., concentrated hydrochloric acid, 25 c.c., and water, 800 c.c.) was added. The mixture was then put into a shaker for about half an hour. A considerable number of extractives were tried for removing the urobilin from the stools, but none were found as efficient as alcohol with hydrochloric acid. After thorough mixing in the shaker an equal quantity of a saturated solution of zinc acetate in alcohol was added and the mixture was filtered. After adding 2 c.c. of Ehrlich's reagent to 20 c.c. of the filtrate, the solution was put aside in a dark place until next day. The addition of zinc acetate is not absolutely essential, but in some cases we observed an intensification of the urobilin band following its use, and it is perhaps an advantage to make the urine and stool readings, as far as possible, under the same conditions. The development of the urobilinogen band was not always complete until six hours had elapsed, but thereafter there was no loss of urobilinogen or urobilin for a long time, although this was not the case with the zinc acetate filtrates before the addition of Ehrlich's solution. The reading was made in the same way as with the urine and the total amount calculated for the volume of stool after grinding up with water, the dilution of the 25 c.c. by acid alcohol and zinc acetate being taken into account. Instead of using tap water for dilution of the final extract, 60 per cent. alcohol was required to avoid the development of a precipitate.

Bile. A measured amount of bile was mixed to a paste in a mortar with Fuller's earth and left for some hours. An equal amount of the alcoholic solution of zinc acetate was then added and the mixture filtered under pressure, and the remainder washed with measured amounts of zinc acetate alcohol. In this way almost all of the bilirubin was absorbed, and though no doubt there was some loss of urobilinogen and urobilin, the comparatively small amounts found in the washings compared with the quantities present in the first filtrate seemed to indicate that the Fuller's earth had very much less capacity for absorbing urobilin than

bilirubin. Small amounts of urobilin or urobilinogen could no doubt be overlooked by this method. The Ehrlich's solution was added in the same proportion as in the urine but the dilutions had to be made with alcohol instead of water.

Blood Serum. We have tried various methods, but so far we have not been successful in demonstrating urobilin with certainty.

5. THE EXCRETION OF UROBILIN IN URINE

Urobilin is a normal constituent of the urine but the amount is so small under ordinary conditions that it can only be demonstrated by extracting large quantities of urine.

With the methods we have used, a positive result in twenty-four-hour specimens of urine indicates an abnormal increase over the amount usually present. We have only very rarely been able to find a faint and doubtful degree of absorption in the region of the urobilinogen or urobilin bands in the urines of people in apparent health. When, therefore, urobilin is spoken of as being absent from urine, it is understood that an absence of an increased amount of urobilin is meant.

Saillet found in two normal individuals that the quantity of urobilin excreted during the eight hours of sleep was only about one-tenth part of the total twenty-four hours' amount. He gives two curves of the excretion during the day time which show some relation to the body temperature variations. He suggests a connection with the processes of digestion and of general metabolism.

In a case of bronzed diabetes with a large urinary excretion of urobilin we had an opportunity to study the excretion from hour to hour. The patient was on a von Noorden strict diet plus 50 gms. of bread. His habits were very regular. He rose at 7 A.M. and went to sleep at about 9 P.M. Urine was passed every two hours during the day time, and the amount of urobilin determined at once. The amount passed during the six to eight hours of sleep was kept in the dark and the urobilin determined at the earliest opportunity. In such freshly passed specimens, practically all the urobilin is in the form of urobilinogen and the probable error arising from the assumption that the urobilinogen and urobilin

readings represent equivalent values is avoided. For over a month the two-hour excretion was determined every day, with the result that there was invariably found to be a marked diminution in the amount excreted at night. The following is an example of the excretion during three consecutive days.

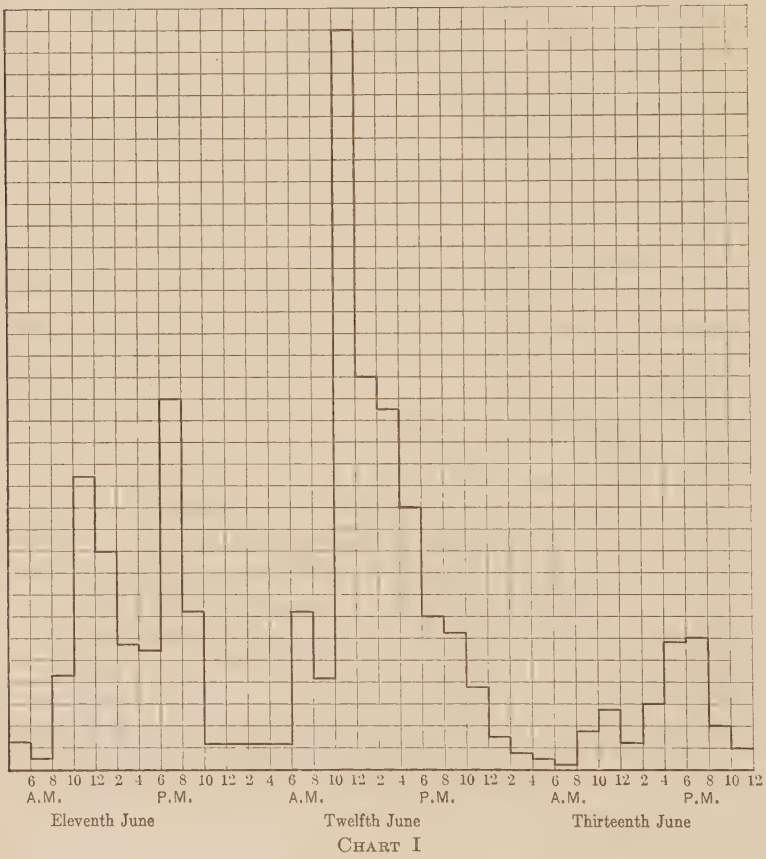


CHART I

The chart is typical of the results throughout the whole period. It shows the decrease of urobilin in the night urine and the great variation in the quantity from day to day and from hour to hour. The only constant feature is the fall during the night. Otherwise there is complete irregularity and the hour of maximum elimination occurred at any time during the day.

When the patient remained up and took his meals during the night and slept in the day time, the amount excreted in the night was much larger than in the day.

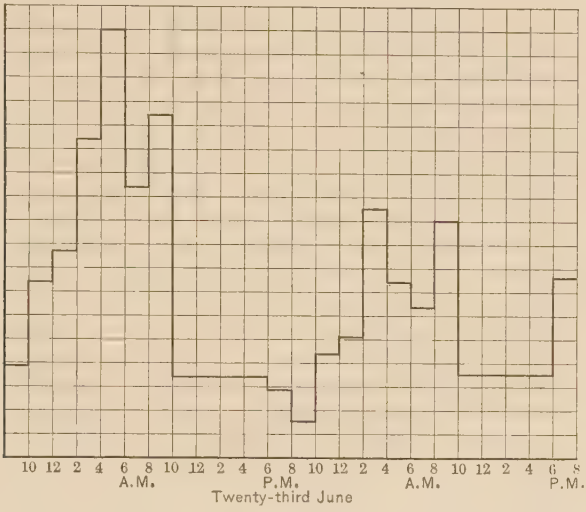


CHART II

The following charts show the relation between the excretion of water, total solids, sugar, chlorides, and urea and urobilin. The relation was only a very general one, for the urobilin excretion shows irregular and wide fluctuations.

These results appear to us to be of interest in connection with the question of urobilin excretion by the kidneys. It is generally agreed that most of the urobilin is formed in the intestine and is carried by the portal vein to the liver. There it is supposed to be either broken down further or resynthetized to bilirubin or hemoglobin (Brugsch) except for a very small part which is carried into the general circulation and is excreted through the kidneys. Where the liver is diseased, the destruction or rebuilding of urobilin fails more or less, so that a greater quantity of the urobilin absorbed from the intestine passes by the liver to the kidneys.

The wide fluctuations in the quantities of urobilin in this case can scarcely be due to variations in the amount of absorption from

the intestine. It is true that bile enters the duodenum only at intervals, but they are regular intervals when the periods of digestion are regular, and on these charts no signs of any periodicity

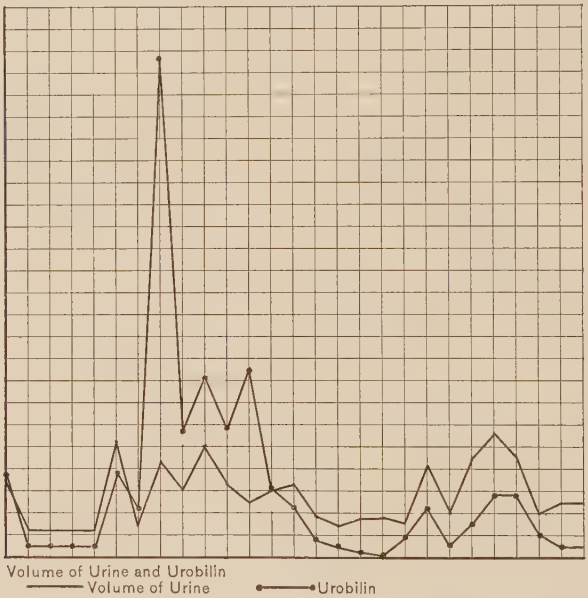


CHART III

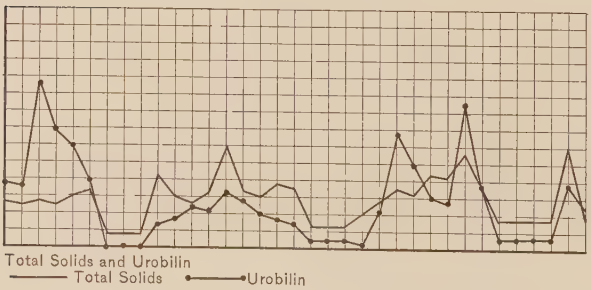


CHART IV

during the day time can be traced. In any case, the bile passes through the small intestine in about four hours, and as our findings as to the amount of urobilin in various parts of the intestinal tract

show, the greatest quantity of urobilin is in the large intestine not in the small. Urobilin is always present in the large intestine and

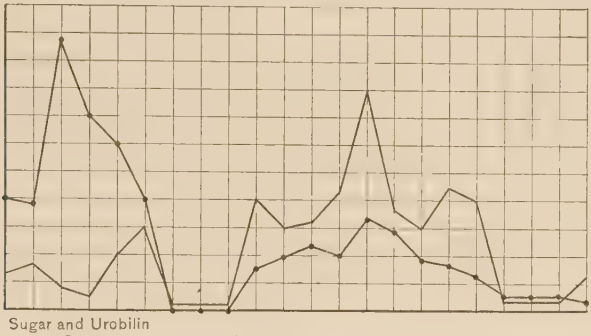


CHART V

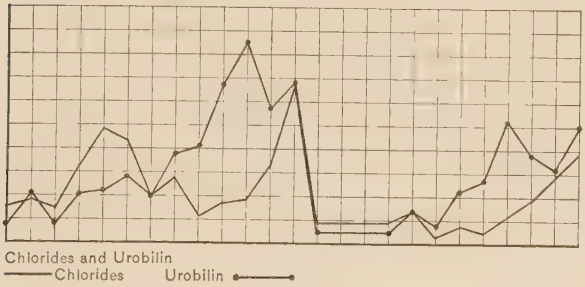


CHART VI

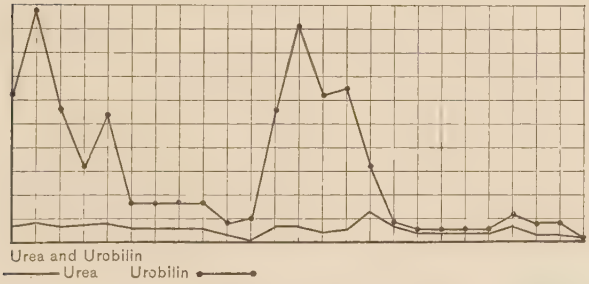


CHART VII

from this situation one could not expect any considerable changes from hour to hour in the amount absorbed. Urobilin is a readily

diffusible substance and since water is removed from the large intestine, it seems probable that urobilin will also be taken up by the blood.

Nor does it seem that changes in the excretory function of the kidneys can account for more than a small part of the urobilin variations. The amounts of sugar and chlorides fall during the night mainly because their absorption from the alimentary canal almost ceases and not because there is any marked decrease in the eliminating functions of the kidneys. But urobilin is present in the large gut in as large amount during the night as during the day, and if absorption is uniform one would expect uniform excretion, or at least no greater variation than might be ascribed to alterations in the circulatory and nervous mechanism of the kidneys. We have no evidence of any specific diminution in excretory power of the kidneys for any substance during the night.

If the absorption and excretion of urobilin appear to be too continuous and uniform to explain these charts, can we regard the variations shown in them as indicative of fluctuations in the power of the liver to keep the urobilin reaching it from the intestine from entering the general circulation?

The patient had an extremely large liver which postmortem was found to be cirrhotic and to contain a large amount of the pigment found in cases of hemachromatosis. During the day when the work of the liver was increased because of the absorption of food products, it might be imagined that the liver would be less able to cope with the urobilin brought to it, and the great increase during the daytime might be thus explained. But the wide and irregular fluctuations from day to day and from hour to hour in spite of the fact that the meals were taken at regular intervals, remain to be accounted for. Possibly some other factor such as a formation of urobilin in the diseased liver may have played a part. In Saillet's two curves of hourly urobilin excretion in people in health, no such wide variations are to be seen.

Other possible factors which may play a part in alterations of the urinary excretion of urobilin are the changes which urobilin undergoes in the blood and tissues. The form in which urobilin circulates in the blood stream is still unknown, and the question

as to whether it may not there in part be broken up or synthetized to some other substance, or may not be stored in some form or other in the tissues is still unsolved, and it is possible that in them an explanation may be found for these anomalies of urobilin excretion. At present they can only be recorded.

6. THE EXCRETION OF UROBILIN IN THE STOOLS

In the following ten adults in whom there was no reason to suspect any disturbance of hemoglobin metabolism, the average daily excretion in the stools was worked out.

Length of period of observation.	Diagnosis.	Average daily urobilin in stools.
8 days	Inguinal hernia	8685
15 days	Fractured femur	3855
3 days	Chronic appendicitis	6080
3 days	Endometritis	3307
6 days	Neurasthenia	4887
10 days	Neuritis	8702
15 days	Chronic arthritis	6604
11 days	Neurasthenia	8737
6 days	Fractured femur	5840
6 days	Fractured tibia	8053

These cases, therefore, showed variations between 3307 and 8737 and a general average of 6475.

The impossibility of gaining any idea as to the amount of urobilin excreted in the stools by an examination of a single twenty-four hours' collection is apparent when the figures for the daily excretion of any of the cases we have worked with are examined.

Day.	Patient A.	Patient B. Urobilin in stool.	Patient C.	Patient D.
1st	2,408	4,800	16,640	5,120
2nd	10,880	3,360	5,280	13,440
3rd	no stool	3,840	7,680	2,560
4th	7,360	960	1,440	no stool
5th	4,480	no stool	4,800	3,840
6th	1,280	6,080	15,360	14,400
7th	7,680	10,240	25,920	no stool
8th	4,000	8,000	8,320	35,200
9th	no stool	no stool	3,840	1,536
10th	720	3,200	5,760	3,200
11th	7,040	11,200	6,720	7,040

The variations, it is seen, are sometimes very large indeed.

To a certain extent, of course, this is accounted for by differences in the quantity of feces passed from day to day, but there are certainly other factors involved. We were particularly struck with the fact that on the days following a period of twenty-four hours, during which no stool was passed, there was not, as a rule, any increase in the urobilin. If the urobilin in the stools retained in the large intestine were absorbed by the blood stream, one would have expected an increase in the urobilin in the urine on these days. But on reviewing the figures, no constant increase in the urobilin in the urine could be established. We were then inclined to attribute this apparent loss of urobilin to destruction within the gut. However, when the effect of keeping stools in an incubator at 37° C. was tried, we found to our surprise that there was no loss of urobilin.

The stools were thoroughly ground up in water and kept in the incubator. Every day, 25 c.c. were removed and extracted with acid alcohol. With the exception of the last stool, the figures show only such differences as lie within the limits of error of the method. There was only a slight diminution of urobilinogen and increase of urobilin.

Fresh stool.	After 24 hours.	After 48 hours.	After 72 hours.	After 96 hours.
15	16	16		
3	3	2	3	3
12	19	14	18	11
57	62	65	66	65
20	21	20	18	24
60	55	48	53	60
3	3	3	4	4
65	60	55	51	48

So long then as stools are kept from exposure to light there does not seem to be much loss of urobilin. Later experiments seem to indicate that concentration by evaporation may have been responsible for the apparent retention of the original urobilin value. At the end of seven days in tightly corked vessels about one-quarter of the total urobilin value had been lost. Nor on the other hand is there any increase such as might have occurred if the

formation of urobilin in the freshly passed stool had been incomplete.

The absence of extensive destruction of urobilin in stools kept under these conditions outside the body, does not of course preclude the possibility of such an action taking place within the bowel, where absorption and excretion are proceeding and where there is no exposure to air. It was thought that an indication of such a loss of urobilin either by absorption or destruction was obtained when the relative amounts of urobilin present in the contents at different levels of the intestinal tract were compared.

The feces obtained postmortem in 5 cases were ground up in so much acid alcohol as gave, so far as could be seen, an approximately equal consistency. The relative amounts of urobilin were as follows: Duodenum, 1; jejunum, 1.2; ileum, 4.8; cecum, 12.3; descending colon, 5.5.

The relative decrease in the descending colon as compared with the cecum certainly suggests a loss of urobilin, but the number of cases examined was too small to permit of any definite conclusion. In all probability, both absorption and destruction are at work. The absence of increased urobilin in the urine on the days of constipation is not by any means conclusive evidence against the occurrence of absorption of urobilin from retained stools, for the absolute want of any relationship between the amount of urobilin in the stools and in the urine is a fact which must impress anyone who makes such concomitant observations. No doubt, the quantity in the intestine is a factor in determining the amount excreted by the urine, but except under conditions such as an unusually large hemoglobin destruction, when there may be a very great increase of urobilin in the stools, its effect is altogether overshadowed by other influences at work on the urobilin in its passage through the blood stream, liver, bile, tissues, and kidneys.

The interpretation of the results of urobilin estimations in the stools is a comparatively simple matter when compared with the complexities and obscurities surrounding the question of the elimination of urobilin in the urine, and we believe that, from a clinical point of view, work on the stools will give results of much greater

value and of much less doubtful significance than has been the case up to the present, when the attention of clinicians has been directed practically exclusively to the urine.

Our own experience in cases of pernicious anemia, and the reports of Simpson in cases of malaria have convinced us that, if constipation or diarrhea are avoided, the determination of the average stool urobilin over a period of several days, is the best guide we have to the quantity of hemoglobin which is being broken down in the body. Its importance in anemias and in all cases where excessive blood destruction is suspected does not need to be elaborated.

7. THE EXCRETION OF UROBILIN IN BILE

Urobilin has been found in human bile postmortem by Jaffe, Müller, Tissier, Gerhardt, Beck, and Braunstein. After the introduction of Ehrlich's reagent, urobilinogen was found in 43 of 46 cases by Kimura. Neither is constantly present, for in cases in which severe diarrhea had occurred or in which there had been obstruction to the flow of bile into the intestine they were not found. Austin and Ordway in a very careful study found urobilin present in 94 per cent. of 50 cases with biliary fistulas in which urobilin was present in the stools and urine. In 7 cases in which no urobilin could be demonstrated in either the stool or urine, urobilin was present in the bile in two. Fischler found urobilin in the bile of normal dogs. After establishing a biliary fistula and obstructing the common bile duct, urobilin disappeared from the bile, but it was still found, though in diminished amount, in the stools. When the liver was damaged by amyl alcohol urobilin appeared in considerable amounts in the bile. He believes that the only way in which this can be accounted for is by assuming that the urobilin was formed in the liver itself.

Our experience with bile removed postmortem goes to show that the amountof urobilin is extremely variable. In the following cases the value of the urobilin in 10 c.c. of bile is given.

	Dilution value in 10 c.c. bile.
1. Pernicious anemia	3940
2. Pernicious anemia	80
3. Pneumococcal meningitis	2100
4. Pyonephrosis	4500
5. Bronchopneumonia	650
6. Streptodiplococcal septicemia	0
7. Cerebral embolism	620
8. Aneurysm	300
9. Aortic incompetence	45
10. Diabetes	200
11. Bronzed diabetes	1800
12. Carcinoma of liver (without duct obstruction)	45
13. Tetanus	0
14. Carcinoma of larynx	0
15. Hypophysis tumor	0
16. Adherent pericarditis and valvular disease	0

Of the 16 cases there were 5 in which no urobilin was found by the method we used. But if larger amounts of bile had been used for extraction we might have found traces, and we therefore cannot say more than that the quantity was at least very small. No relation was found between the length of time after death before the bile was examined and the amount of urobilin found. In one case urobilin to a dilution value of 1800 for every 10 c.c. of bile was present, although it was removed from the body within three-quarters of an hour after death. It does not seem that postmortem decomposition of bilirubin can possibly explain the variations in quantity which were found.

On the other hand there is no obvious connection between the nature of the disease and the amounts obtained. We are inclined to believe that the degree of absorption of urobilin from the intestine just before death is an important factor. In the two patients with pernicious anemia estimations of the amount of urobilin present in the intestinal contents were made, and an enormous quantity was found in the case which contained so much urobilin in the bile, and comparatively little in the one which showed a low dilution value. In another case in which severe diarrhea had completely emptied the intestine no urobilin could be detected in the bile. In a dog which died four days after the common bile duct had been severed and in whose intestines no urobilin was found, there was also no urobilin in the bile, although it was found in the bile of normal dogs. These observations bear out the well-recognized

importance of the intestinal source of biliary urobilin, and yet exceptions are sufficiently striking to make one hesitate to accept the exclusively enterogenous origin of urobilin.

In a few cases with biliary fistulas after operations for gall-stones the urobilin in the bile was found to increase as the bile began again to enter the intestine, but there was no definite qualitative relationship between the amount in the bile and in the stools. An exception was found in one patient, whose case is discussed later, in whom urobilin was present in large amount in the bile while urobilin was practically absent from the stools. This was a case of gall-stones in which for a period of eight days after a gall-bladder fistula had been established, the total urobilin in the stools amounted to only 720 dilutions while in the bile an amount equivalent to 35,144 dilutions were found. The stools contained no more urobilin than we found in a case in which there was undoubtedly a complete occlusion of the common duct. Probably no bilirubin at all was entering the intestine. Later on when the bile again passed through the common duct the urobilin increased in amount in the stools to 33,216 dilutions in seven days, but the percentage of urobilin in the bile which still came from the fistula for the first four days of this period was only 230 dilutions for each 100 c.c. of bile, in contrast with 1360 where there was practically no urobilin in the stools. In cases of this sort it is difficult to avoid the conclusion that the urobilin has been formed in the liver itself.

8. UROBILIN IN THE BLOOD

Urobilin is present in the intestine and is excreted in part by the kidneys. It presumably reaches the kidneys by means of the blood. One would expect to be able to detect it in the blood of those not infrequent cases in whom even more urobilin is found in the urine than in the stools. Yet there is no point in the whole subject on which there is more diversity of results and of opinions. The constant absence of urobilin in the serum in cases of urobilinuria was a main support of the theory advanced by Gilbert and Herscher that urobilin was formed from bilirubin during excre-

tion through the kidneys. Even long after the inadequacy of this hypothesis had been exposed by the work of von Müller and the intestinal origin of the urobilin of the urine had been generally accepted, no one was able to demonstrate the presence of urobilin in the blood or serum. Müller and Gerhardt believed that it was not present in appreciable amount in the blood and Schlesinger reported 15 cases of very marked urobilinuria whose sera gave a negative reaction for urobilin.

It was not until 1906 that Huber published a report in which he stated that urobilin was always found in serum when urobilin was present in the urine. He ascribed the negative results of Schlesinger to the fact that he had not added Lugol's solution to the zinc acetate filtrate in order that urobilinogen might be oxidized to urobilin. But considerable doubt was cast on Huber's results when it was pointed out that the green fluorescence characteristic of urobilin might be very closely imitated by biliverdin, and that especially after the addition of Lugol's solution, the bilirubin normally present in serum might be oxidized to biliverdin. Biffi (1907) extracted oxalated blood with chloroform and examined the filtrate spectroscopically and found urobilin present in small quantities in a number of cases. He stated that in lobar pneumonia it was almost constantly found. Moller (1909) could not confirm Biffi's findings as to the relative frequency of a positive reaction for urobilin in serum, but with the zinc acetate and Lugol's solution found it in only two cases, both of lobar pneumonia, and later with Biffi's method in two other cases of pneumonia and one of pernicious anemia.

Further evidence of the occurrence of urobilin in serum was given by v. Jaksch who stated that in fatal cases of pneumonia the serum separated from blood removed by venesection showed a green fluorescence which disappeared on exposure to light. Conner and Roper (1909) in a study of the relation between the bilirubin in serum and urobilin in the urine, repeatedly and carefully examined the sera of over 60 patients with urobilinuria, with uniformly negative results, until the serum of a patient dying of lobar pneumonia was met with. This serum gave a markedly positive reaction for urobilin with all the methods. In 9 other

cases of pneumonia shortly before death the serum contained large amounts of urobilin. In 3 severe cases of pneumonia who recovered urobilin was detected in small amount in the serum, but in 15 others who lived no urobilin was found. There was no parallelism between the amount of urobilin in the serum and in the urine.

Lehndorf (1913) could find urobilin only in two of the sera he investigated. One was from a case of decompensated mitral stenosis and the other from a case of myocardial degeneration with pleurisy shortly before death. Fromholdt and Nersessoff (1912) by a somewhat complicated method and by extracting relatively large volumes of oxalated plasma were able to demonstrate urobilin in the serum of 7 out of 11 cases with urobilin in the urine. They record a doubtfully positive reaction in a case of occlusion of the common duct with no urobilin either in the stools or the urine. The spectroscopic band of urobilin became unmistakable after the addition of iodine, but they are inclined to think that this may possibly have been due to a conversion of bilirubin into urobilin.

Hildebrandt (1909) who after many negative results found the spectrum of urobilin in the serum of a case of pneumonia shortly before death, believes that urobilin normally circulates in the blood as urobilinogen, because in this case the urobilin band only appeared after the serum had been exposed for some time to light and air. He got a red color on mixing Ehrlich's reagent with the serum before the urobilin had appeared. Moller, though he is inclined to agree with Hildebrandt, points out the technical difficulties of urobilinogen recognition in serum since the hydrochloric acid precipitates the proteins. He got an apparently positive reaction in only two of his cases. In 3 cases Conner and Roper showed the characteristic red color and confirmed the presence of urobilinogen by finding the absorption band of the benzaldehyde compound. But in the other cases in which urobilin was present they did not find any urobilinogen.

Conner and Roper's spectroscopic recognition of urobilinogen is the only observation which can be taken as approaching to a proof of the presence of this body in serum, and in view of the substances of the indol group, which may give a spectrum very

similar to that of the urobilinogen compound, their statement cannot, in the absence of any data as to the exact position of the absorption band, be taken as decisive.

In fact, the evidence so far points in just the other direction and seems to indicate that urobilin instead of circulating in the reduction form of urobilinogen is present as an oxidation product which does not possess the spectroscopic characteristics of urobilin and so escapes detection. This evidence is all the stronger because it has been collected independently by three observers since 1903, none of whom apparently knew about each other's work. Schlesinger finding no urobilin in the blood of cases in which he expected it, tried the effect of adding urobilin to serum and to blood. He discovered that whereas it was readily demonstrated in the serum, it disappeared in the whole blood or in serum to which red blood cells had been added. Clarens made the same observation, and in 1911 Roth and Herzfeld confirmed Schlesinger's experiment and suggested that the disappearance of the urobilin might be due to oxidation.

They found that oxygenated serum destroyed the urobilin and that in whole blood its disappearance might be delayed by carbon dioxide. In a few cases, though not in all, they were able to demonstrate the presence of urobilin in serum after it had stood for twenty-four to forty-eight hours mixed with finely powdered zinc. Since urobilinogen is found in the urine of cases in which no urobilin can be found in the serum, it seems that the kidneys must possess the faculty of reducing the oxidized urobilin. They were only able to carry out two experiments with kidney extracts, one of which gave a definite production of urobilin in a serum in which it had previously been found absent. It is noteworthy that urobilin was formed with an alcoholic kidney extract, so that the process cannot depend on any vital activity in the cells.

The conception of the oxidation of urobilin in the blood stream is strengthened when it is remembered that the only cases in which urobilin has been with certainty found in the serum are those in which there was a great reduction in the available oxygen of the blood. They have been almost without exception cases of lobar pneumonia shortly before death.

The effect on urobilin of the blood and tissues opens up a new field for investigation, and it is not improbable that along these lines facts may be discovered which will throw light on the present obscurity.

9. ANIMAL EXPERIMENTS

The Excretion of Urobilin in Animals. No satisfactory estimations could be made on the stools of rabbits or goats because the amount of urobilin was too small.

The same difficulty, though to a lesser extent, was encountered in dealing with the excreta of cats and dogs. Even when the extract was made as concentrated as possible it seldom required more than a few dilutions to obliterate the spectra of urobilinogen and urobilin. We have not been able to find any systematic investigation of the pigments of the stools of dogs or cats, but it is known that cholecyanin (Fischler, Inaug. Diss., p. 84) a derivative of bilirubin which is not regularly present in human stools, is constantly found. Possibly the greater part of the bilirubin in the intestine of these animals may be excreted in other forms than urobilin. Certainly the acid alcohol extracts of the stools contained a large amount of light absorbing material, so much so as to render the urobilin band somewhat obscure at the low dilution at which it had to be read. And not infrequently other absorption bands were seen. The method did not then give such definite and clear results as were obtained with human stools.

It was soon found that such small amounts of urobilin as were detected varied considerably from day to day. No satisfactory explanation for this variation was obvious, but one possible factor appeared to be the length of time during which the feces remained in the intestine. Hard constipated stools as a rule contained very little urobilin. The following experiment shows how markedly the quantity of urobilin increases during regular action of the bowels as compared with a period of constipation.

Dogs B, C and D were normal. Dog A had had a biliary fistula and a closure of the common bile duct. At the time of this experiment the fistula was closed and the common duct was again patent.

Urobilin was present in the urine and was added to the amount in the stools. The figures represent the total dilution value of the urobilin excreted during ten days. In the first period the dogs were constipated, in the second sufficient cascara was given to obtain a stool every day without giving rise to marked diarrhea.

	First period of ten days.		Second period of ten days.	
	Urobilin.	Number of stools.	Urobilin.	Number of stools.
Dog A	5,640	4	13,120	10
Dog B	14,400	8	19,200	10
Dog C	9,200	5	16,420	10
Dog D	12,860	7	37,200	9

In these four dogs the total urobilin during the period of constipation was 42,100 and in the period during which cascara was given 85,940, more than twice as much. During another ten-day period castor oil was given, and the total amount passed was 51,250, but regular daily movements were not obtained. Constipation, therefore, in dogs diminishes the amount of urobilin in the stools. We are satisfied that this is true for man also, though we cannot bring forward any systematic evidence. The diminution may be due either to increased absorption of urobilin from the intestine or to destruction of the urobilin. If increased absorption were the cause, the excretion of urobilin in the urine should be increased. In normal dogs or cats urobilin was never found in the urine in sufficient amount to estimate. But in dog A, whose common duct had been tied and a biliary fistula made, it was found six months later that communication between the bile ducts and the intestine had become reëstablished and that the fistula had closed. In this animal considerable amounts of urobilin were constantly present in the urine. The cause of this was found at death to be an extremely marked cirrhosis of the liver which had developed probably as a result of infection through the fistula combined with the initial bile stasis.

Increased absorption during constipation might be expected to show itself in a rise of urobilin in the urine in this case. Yet we were not able to establish any such increase in urinary excretion.

Dog A

Date.	Urobilin in urine.	Urobilin in stool.
December 2	160	No stool
December 3	248	800
December 4	192	800
December 5	224	No stool
December 6	21	400
December 7	100	No stool
December 8	160	No stool
December 9	120	No stool
December 10	240	No stool
December 11	400	1200
December 12	520	No stool
December 13	240	No stool
December 14	280	800
December 15	80	No stool
December 16	200	800
December 17	600	No stool
December 18	160	No stool
December 19	680	400
December 20	480	No stool
December 21	500	No stool

The average amount of urobilin in the urine of the seven days in which urobilin was lost from the body in the stools was 273, and 272 in the thirteen days during which urobilin was retained in the intestine. This evidence would have been more convincing if we had succeeded in contrasting a period of regular evacuation with a period of constipation, but on giving cascara it was found to be impossible to be sure of excluding contamination of the urine with the stools. Still if the figures for the four days from December 3 to December 6, inclusive, during which three stools were passed are contrasted with those from the seventh to the tenth when there were none, it is seen that a total of 685 dilutions of urobilin were present in the first period, and only 620 when the bowels did not act at all.

It seems, therefore, probable that destruction of urobilin plays a much larger part than increased absorption in the diminution of urobilin which occurs during constipation.

Diarrhea, unless it is so pronounced as to lead to the excretion of unaltered bile, does not seem to have nearly so great an influence in diminishing the quantity of urobilin.

The total excretion of urobilin per kilogram of body weight in dogs who had been kept under exactly the same conditions and on the same diet for a long time was determined over a period of forty-one days.

	Kilo. weight.	Dilution value per kilo of body weight.
Dog C	7.82	6100
Dog B	9.95	5220
Dog D	17.80	5450

Dog A, with cirrhosis of the liver, which was also kept under the same conditions for the same time, and which during that period exhibited no obvious signs of ill-health, weighed 4.02 kilo and excreted urobilin with a dilution value of 8806 per kilo body weight. This is an increase of 58 per cent. over the average excretion of urobilin in the three normal dogs. It does not seem probable that an increased hemoglobin metabolism could account for this. It appears much more likely that there was either a diminished destruction of urobilin or an increased formation of urobilin from bilirubin. Constipation was present to a more marked degree in this dog than in the others, so that the increase of urobilin was probably even more marked than the figures suggest. A diminished destruction, if such occurred, must have operated in the body itself. If one of the functions of the liver is the synthesis of urobilin absorbed from the intestine into bilirubin, an explanation of the increase in urobilin excretion is afforded by the supposition that the diseased liver in this case allowed much of the absorbed urobilin to pass through it into the general circulation to be excreted in the urine. But the possibility of the increase in urobilin being due to a formation if urobilin from bilirubin in the diseased liver cannot be excluded. Outside the body we found that urobilinogen and urobilin were produced in considerable amounts in bile left at a temperature of 37° C. And it seems possible that such a breaking down of bilirubin may occur in stagnating bile, especially if an infection of the bile passages exists.

THE EFFECT OF COMMON DUCT CLOSURE

In attempting to follow the effect of closure of the common bile duct in dogs on the urobilin excretion, a difficulty was met with in connection with the methods we used. In the acholic stool extracts a pink color was produced which apparently showed the spectroscopic absorption of urobilinogen. That in reality

it was some other substance was shown by the difference in the color reaction with Ehrlich's solution and also by the fact that on exposure of the zinc acetate filtrate to light the absorption band still persisted instead of disappearing. In all probability this substance was indol or some derivation of indol. V. Morsacsewski found that in acholic stools there is an increase in indol which has an absorption band very similar to that of urobilinogen.

To avoid confusion with this substance we have taken no account of the urobilinogen either before or after the closure of the common bile duct. This makes the total amounts given inaccurate, but our object was to see whether the absence of bile from the intestine would completely stop all excretion of urobilin or not. As is seen from the two experiments below, urobilin disappears for a time, but it afterward returns in diminished, though relatively not inconsiderable, amount in the stools. In both these cases also urobilin after an interval was found in the urine. The impossibility of obtaining urobilin free stools in dogs even though all bile is prevented from entering the intestine has been noted by Fischler. Brugsch and Yoshimoto in a dog with biliary fistula found that urobilin reappeared after an interval in the stools.

Dog E. Section of common duct removed.

Icterus, acholic stools, and bile in the urine appeared. At postmortem a distended gall-bladder and ducts were found. No communication with the intestines. A few patches of organized lymph were found on the liver and adhesions around the resected duct but no general peritonitis. Urobilin is given as total amounts in periods of six days.

Before Common Duct Closure

	Stools.	Urine.
First period	3200	0
Second period	2320	0

After Common Duct Closure

	Stools.	Urine.
Third period	0	0
Fourth period	512	185
Fifth period	32	56
Sixth period	320	0
Seventh period	160	76

Dog F. Section of common bile duct removed.

Uninterrupted recovery with development of jaundice. At postmortem the gall-bladder and ducts were found to be greatly distended. There was no communication between them and the intestine. The urobilin is given as a total of estimations of dilution values for the stools and urine passed in periods of six days.

Before Common Duct Closure

	Stools.	Urine.
First period	9312	0
Second period	5120	0

After Common Duct Closure

	Stools.	Urine.
Third period	0	0
Fourth period	0	0
Fifth period	576	396
Sixth period	2368	1084

THE EFFECT OF COMMON DUCT CLOSURE AND BILIARY FISTULA

In three other dogs the common duct was obstructed and a biliary fistula established. No jaundice developed.

Here also the amount of urobilin in the stools decreased, but did not disappear. Urobilin appeared in the urine of dog A, which was afterward found to have developed a cirrhosis of the liver. In the other two it was absent. The urobilin is given as the total dilution values of six-day periods.

After death no communication was found between the bile passages and the intestine in dogs G and H.

Before Common Duct Closure and Biliary Fistula

Dog G.	Stools.	Urine.[1]
First period	1920	0
Second period	1590	0
Third period	3524	0

After Common Duct Closure and Biliary Fistula

Fourth period	240	0
Fifth period	1845	0
Sixth period	560	0
Seventh period	384	0

[1] Urobilin was occasionally found in the urine, but this was due to contamination with bile. It was at first difficult to prevent the urine wetting the dressings and taking up some of the bile which was rich in urobilin.

Before Common Duct Closure and Biliary Fistula

Dog H.	Stools.	Urine.
First period	1744	0
Second period	930	0
Third period	632	0

After Common Duct Closure and Biliary Fistula

	Stools.	Urine.
Fourth period	64	0
Fifth period	176	0
Sixth period	688	0

Before Common Duct Closure and Biliary Fistula

Dog A.	Stools.	Urine.
First period	3480	0
Second period	3256	0

After Common Duct Closure and Biliary Fistula

	Stools.	Urine.
Third period	728	0
Fourth period	520	22
Fifth period	280	68
Sixth period	1260	26
Seventh period	632	239
Eighth period	720	...

DISCUSSION

The presence of urobilin in the stools after closure of the common bile duct cannot be explained as due to the excretion of bilirubin into the intestine from the blood, for it was also found in the stools of the dogs in which the bile was allowed to drain out of the body and in which there was no increase of bilirubin in the blood. The only possible explanation seems to be that urobilin itself was excreted from the blood into the intestine. Where was this urobilin produced? Urobilin is known to have formed in old hematomas in various parts of the body, so that the formation of urobilin from bilirubin in the tissues of the icteric dogs is a possibility. But the fact that it also was found in the excreta of dogs who were not jaundiced points to the liver as the place of formation, for in the biliary fistulas of dogs this was the only organ in which bile was present. Urobilin was found in the bile escaping from the fistulas.

We must conclude then that in dogs the intestine is not the only

site of origin of urobilin, but that under certain conditions urobilin is formed in the liver. Whether this is a normal function of the liver or not is another question which will be discussed later.

These experiments, though few in number and inconclusive in their results, are yet sufficient to show the complexity of the subject and the number of factors which may play a part in excretion of urobilin. Variations in the amount of formation of urobilin in the intestine or in destruction after it has been formed, the degree of absorption from the intestine, the fate of the absorbed urobilin in the liver, whether it is rebuilt to bilirubin or is allowed to pass into the general circulation, the question as to a change of bilirubin into urobilin in the liver under certain conditions, and the possibility of the excretion of urobilin from the blood into the intestine, are some of the points which have to be considered in interpreting the results.

In any case we must conclude that in dogs at least the theory of the exclusively enterogenous origin of urobilin does not suffice to meet the facts.

10. CLINICAL REPORTS

To enumerate all of the conditions in which urobilin has been found in excess clinically does not seem to us desirable, as we wish to point out the significance of its occurrence in the few where its clinical study has been found to be of most value. The following clinical reports are selected from a series of observations made by us during the last two years.

DISEASES OF THE LIVER WITHOUT MUCH, IF ANY, INTERFERENCE WITH THE ENTRANCE OF THE BILE INTO THE INTESTINE

Case.	Length of period of observation.	Diagnosis.	Average daily urobilin. Urine.	Stools.
I. N.	53 days	Portal cirrhosis	572	3647
A. F.	10 days	Portal cirrhosis	241	3088
C. D.	14 days	Cirrhosis (syphilitic)	456	3451
C. B.	30 days	Bronzed diabetes	5800	7400
F. M.	4 days	Hanot's cirrhosis	2034	3360
F. O'B.	15 days	Abscess of the liver	1713	4047

I. N. Enlarged liver with ascites.

Red-blood cells, about 3,000,000, and hemoglobin, 55 per cent. Remained during the time of observation in about the same condition. Fluid was removed from the abdomen on several occasions. Urobilin was never found in it. There was a slight grade of jaundice, the serum on one occasion showing six times the normal amount of bilirubin. One month after the estimations were discontinued the patient died and the liver showed a well-marked portal cirrhosis. The accompanying chart shows the urinary and stool excretion of urobilin. The stools were given as averages for periods of three days, to diminish variations due only to changes in the motor activity of the colon and rectum. The considerable variations in the quantities in the stools and the fact that urobilin was not constantly found in the urine are the noteworthy points in this case.

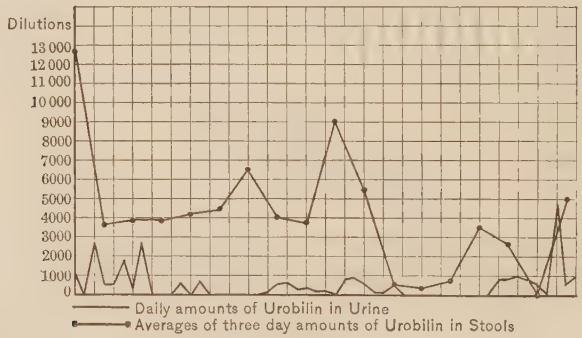


CHART VIII

A. F. A typical case of portal cirrhosis.

C. D. Small liver, large spleen, hematemesis, melena. Glycosuria with polyphagia, polydipsia, and emaciation. Positive Wassermann.

C. B. Very much enlarged liver and spleen. Ascites. Pigmented skin. Glycosuria. At postmortem the diagnosis of bronzed diabetes was confirmed by the finding of a deeply pigmented cirrhotic liver and pancreas. The accompanying chart shows the great variations in the amounts of urobilin in the urine.

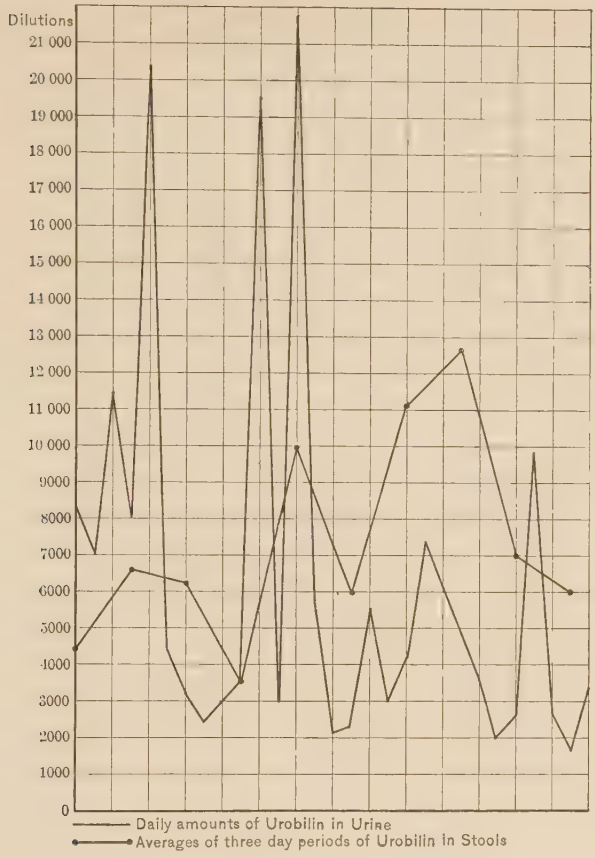


CHART IX

F. M. A man, forty-eight years old, complaining of persistent slight jaundice of two years' duration. No loss of weight. No pain. General health good. Liver greatly enlarged, extends 10 cm. below costal margin. Spleen much enlarged, projects 12 cm. below costal margin. No ascites. Urine contains bile. Red-blood cells, 4,400,000; hemoglobin, 86 per cent; negative Wassermann.

Date.	Urine.	Stools.
November 23	1300	4800
November 24	2950	5120
November 25	1104	960
November 26	2784	2560
	8138	13,440

F. O'B. Admitted with a temperature and polymorphonuclear leukocytosis, complaining of pain and tenderness in the right hypochondriac region. On the eighth day after admission the abdomen was opened and a large abscess of the liver drained.

In this group of cases the urobilinuria is evidently not due to an increased formation of urobilin in the intestine for the quantities found in the stools are not above the normal limits. There is no evidence of any overflooding of the liver by urobilin derived from an increased destruction of hemoglobin. That the abnormal quantity of urobilin in the urine is to be ascribed to the pathological changes in the liver which were present to a marked degree in all these cases, is suggested not only by the constancy of the association of urobilinuria with liver disease, which has been noted by all observers, but also by the fact that in particular cases it is possible to observe the diminution and final disappearance of urobilin from the urine of those cases in which an abnormal condition in the liver is removed. The case F. O'B., with a large liver abscess, was a good example of this. During the week preceding the opening of the abscess the average daily excretion was 2187. For a few days after the operation the quantity in the urine remained high and then dropped so that the daily average for the seven days after operation was only 244.

It will be noted that it is not possible to exclude pronounced disease of the liver by a failure to find urobilin in the urine on one examination. As may be seen from the chart of the case of I. N., who had a very marked cirrhosis of the liver, there was a period of five days, during which no urobilin could be detected. And even in the patient C. B., in whose urine there was as a rule such a large amount of urobilin, none was found in one twenty-four-hour specimen. The fluctuation in the quantity of urobilin from hour to hour and from day to day make it imperative to take the average of a series of twenty-four-hour specimens before an idea can be obtained as to the grade of urobilinuria in any particular case.

The study of a large series of cases of liver disease along these lines, with concomitant estimations of the urobilin in the stools and in association with other tests of hepatic efficiency, will be necessary before it is possible to say whether the degree of

urobilinuria may be taken as an approximate guide to the amount of impairment of liver functions.

Patients in Whom Part of the Bile Entered the Intestine and Part Left the Body through a Gall-bladder Fistula

Case.	Length of period of observation.	Diagnosis.	Average daily urobilin. Bile.	Urine.	Stools.
A. R.	18 days	Cholelithiasis	788	0	4240
B. H.	13 days	Chronic cholecystitis	1050	0	2669

A. R. This case was operated on for the relief of dyspeptic symptoms. No icterus. A thickened gall-bladder containing a large stone was found. The gall-bladder was drained. There was no jaundice following the operation.

B. H. Operated on for symptoms of dyspepsia. No jaundice before or after operation. A moderately thickened injected gall-bladder with adhesions was found and drained. In these 2 cases, there was no obstruction to the flow of bile through the common duct and only a part of the bile escaped from the fistula.

The urobilin found in this fraction of the bile is of interest in connection with the question as to how much of the urobilin is simply excreted again into the intestine after absorption by the portal bloodvessels. To judge from these 2 cases, it would appear that a very large part of the absorbed urobilin is excreted into the intestine unchanged. But it must be remembered that neither of these were normal cases, and that the possibility of the formation of urobilin in the liver itself existed.

Complete Obstruction to the Entrance of Bile into the Intestine

Case.	Length of period of observation.	Diagnosis.	Average daily urobilin. Urine.	Stools.
F. W.	34 days	Carcinoma of hepatic ducts	0	178
G. W.	5 days	Carcinoma of stomach	0	0
A. M.	6 days	Carcinoma of pancreas	0	0
B. M.	3 days	Carcinoma of duodenum	0	0

F. W.[1] This was a case which we have already reported in which there was a large liver, deep jaundice, and clay-colored stools.

[1] Thirty-five grams of dried bile was given to this patient by mouth in an attempt to confirm Müller's experiment in which he succeeded in producing urobilinuria in such cases. No urobilin appeared in the urine, but this may have been due to the form in which the bile was given. Fromholdt also obtained negative results with various preparations of bile and found that it was necessary to give fresh bile as Müller himself did.

Some of the urobilin found may have been derived from bile given by mouth, but it was also found before it was taken and also more than two weeks afterward.

At postmortem, a large carcinomatous mass in the liver was found to have completely obstructed the hepatic duct.

G. W. Jaundice had been present for two weeks before the estimations were made. Afterward, at operation, a pyloric carcinoma obstructing the common duct was found.

Deep jaundice of several months' duration. Postmortem as scirrhous carcinoma of the pancreas was found.

B. M. At operation a carcinoma of the duodenum was found which completely obstructed the ampulla of Vater.

In these 4 cases, no bile was entering the intestine except such traces as might be excreted from the blood. Bile was present in all the tissues of the body and practically the only mode of excretion was through the urine.

The law of the enterogenous theory of the origin of urobilin, that without the entrance of bile into the intestine, no urobilin is formed, is borne out by the last three cases but not by the first.

In itself, we should not have been inclined to attribute much importance to this exception, if it had not been that Fischler and we ourselves had found urobilin in the stools of dogs with closed common ducts and that several observers (Gerhardt, Hoppe-Seyler, Tsuchuya and Fischer, and Meyer-Betz) have even found urobilin in the urine when no bile was entering the intestine.

Our method gives positive results in the urine only when the amount is distinctly larger than normal, so that urobilin may very well have been present. And it is noteworthy that we found urobilin in the fluid removed postmortem from the broken-down cancer tissue in the liver.

In the other three patients in whom no urobilin could be detected in the stools, the liver itself was not directly involved. It seems then, that this case gives some evidence in support of the hypothesis that the diseased liver may itself form urobilin.

PATIENTS IN WHOM THERE WAS OBSTRUCTION TO THE ENTRANCE OF BILE INTO THE INTESTINE AND IN WHOM PART OF THE BILE LEFT THE BODY THROUGH A GALL-BLADDER FISTULA

Case.	Length of period of observation.	Diagnosis.	Average daily urobilin. Bile.	Urine.	Stools.
A. R.	5 days	Cholelithiasis	0	0	0
E. W.	8 days	Cholelithiasis	5856	640	160

A. R. Admitted with typical signs of acute cholecystitis. Slight icterus but no bile in the urine.

The gall-bladder was drained. For the first few days the jaundice deepened and bile appeared in the urine. Thereafter it diminished and on the fifth day after operation the urine was free from bile. On the seventh day no icterus could be detected.

E. W. The patient was operated on for symptoms of gall-stones. There was no jaundice. A stone was removed from the common duct and the gall-bladder drained. After the operation there was deep jaundice, acholic stools, and bile in the urine.

In both of these patients the manipulations during the operation caused a closure of the common duct, and the drainage through the fistula was not sufficiently free to prevent the occurrence of jaundice. There was, therefore, a complete or almost complete obstruction to the passage of bile into the duodenum, combined with the escape of a part of the bile through the gall-bladder fistula.

But though clinically so similar, there is a remarkable contrast in the urobilin figures. The patient, A. R., might be cited as an excellent example in support of the purely enterogenous origin of urobilin, while the case E. W. appears to offer very strong evidence in support of the possibility of the formation of urobilin in the liver under certain conditions.

The subsequent course of urobilin excretion in these two cases appears to be worthy of mention and for this purpose it is most conveniently divided into periods corresponding with changes in the biliary excretion.

In the patient A. R., during the days immediately following the operation, when bile was still present in the intestinal tract, considerable amounts of urobilin were found in the urine and some in the bile.

Period 1

Bile.	Urine.	Stools.
432	1270	0

Thereafter, during the time in which there was jaundice, acholic stools and bile in the urine, no urobilin was found either in the bile or urine.

Period 2

Bile.	Urine.	Stools.
0	0	0

In the third period, the jaundice diminished, the stools became colored, and with this urobilin reappeared in the bile and urine.

Period 3

Bile.	Urine.	Stools.
492	1240	5896

The fourth period seemed to illustrate the effect of recovery of the liver function, for as the patient's condition improved, the urobilin was found to diminish and at last disappear from the urine in spite of the fact that more bile was entering the intestine because of the removal of the gall-bladder drain.

Period 4

Date.	Bile.	Urine.	Stools.
April 1	144	704	0
April 2	18	864	1600
April 3	Drain removed	656	7680
April 4	...	448	8960
April 5	...	0	7680
April 6	...	0	6400

Three weeks later, the patient returned with recurrence of the cholecystitis and at least a partial blocking of the common duct. On May 1, the fistula was reopened, and much bile, mucus, and pus escaped. Urobilin, present at first in very small amounts in the stools, increased in the next few days and urobilin reappeared in the urine and bile. During the whole of the next month, during which the patient was under observation, urobilin was present in considerable amount in the urine, as if during this second attack, the liver had suffered some more lasting damage. Subsequently, though sometimes found in small amounts, it was often absent.

Period 5

Date.	Bile.	Urine.	Stools.
May 1	0	0	160
May 2	0	1224	240
May 3	0	3900	64
May 4	84	4480	Stool lost
May 5	36	7800	19,540
May 6	120	5040	6,784
May 7	224	1700	9,230

This case, therefore, supports what may be called the orthodox theory of the necessity of the presence of bile in the intestine for the production of urobilin and also may be taken as illustrating the effect of damage to the liver on the urinary excretion of urobilin.

On the other hand, the case of E. W. cannot be reconciled with the exclusively enterogenous origin of urobilin and in the clearest instance we have met with, of the necessity of admitting that at at any rate in some cases urobilin may be produced elsewhere than in the intestine.

During a time when the stools were colorless, the skin jaundiced, and the urine laden with bile, that is to say, when everything pointed to the practical absence of bile from the gut, there was a very large excretion of urobilin in the bile and a not inconsiderable amount in the urine.

Period 1

Bile.	Urine.	Stools.
5856	640	160

During the next eight days, urobilin reappeared in the stools and the jaundice diminished, but the urobilin in the bile and urine, instead of increasing as one might have expected, decreased in amount.

Period 2. Average Daily Excretion

Bile.	Urine.	Stools.
1176	592	3625

It seems most probable that in this case the urobilin in the urine during the first period was absorbed by the blood stream from the urobilin in the bile and excreted through the kidneys. The diminution during the second period, in spite of the reëntrance of bile into the intestine, may perhaps be ascribed to a decrease in the formation of urobilin by the liver, as it began to recover its normal functions. In any case, the large amount of urobilin in the bile cannot have been absorbed from the intestines.

If, in such cases as these, a marked urobilinuria may be present in spite of the total or almost total absence of urobilin from the

gut, it would seem to be likely that in all cases of urobilinuria in liver disease, some part at least of the urobilin has an extra-intestinal origin.

DISEASES ASSOCIATED WITH CHANGES IN HEMOGLOBIN METABOLISM

Case.	Length of period of observation.	Diagnosis.	Average daily urobilin. Urine.	Stools.
A. H.	25 days	Pernicious anemia	470	24,977
A. T.	12 days	Pernicious anemia	1058	22,014
E. P..	4 days	Secondary anemia from intestinal hemorrhage	0	2,400
L. S.	4 days	Primary polycythemia	1849	3,240
H. L.	7 days	Secondary polycythemia from asthma and emphysema	806	10,011

A. H. Pernicious anemia.

During the period in which estimations were carried out the red-blood cells varied from 1,300,000 to 1,800,000 and the hemoglobin from 31 per cent. to 38 per cent.

A. T. Pernicious anemia.

The red-blood cells numbered 1,000,000 and the hemoglobin was 28 per cent.

E. P. For eleven years the patient had had bleeding from the bowel. The stools were sometimes tarry, sometimes contained bright red blood. No cause was found even after the abdomen was opened.[1] At the time of observation the red-blood cells varied from 2,100,000 to 2,550,000 and the hemoglobin from 27 to 29 per cent.

Date.	Urine.	Stools.
November 23	0	5120
November 24	0	No stool
November 25	0	2560
November 26	0	1920

L. S. Noticed a bluish tinge in her face and hands three years ago. During the time of observation the red cells numbered from 6,500,000 to 7,500,000 and the hemoglobin was over 110 per cent. No normoblasts were found. There was no splenic enlargement.

[1] Subsequently a Whitehead operation was done because of slight erosions near the anal opening, with complete recovery of the patient. Evidently reverse peristalsis had carried the blood up into the colon, leading to the tarry stools.

Date.	Urine.	Stools.
September 5	4455	800
September 6	1560	8960
September 7	1080	3200
September 8	360	No stool

H. L. Asthma and emphysema since childhood.

Marked and constant cyanosis.

At the time of observation there were 7,350,000 red-blood cells and 120 per cent. of hemoglobin. There was no fever and the general health of the patient was as good as it ever was.

Date.	Urine.	Stools.
September 2	980	8,000
September 3	2016	14,080
September 4	0	11,520
September 5	864	8,000
September 6	0	9,600
September 7	900	4,480
September 8	880	14,400

Pernicious Anemia. The amounts of urobilin in the stools of these two patients on whom a careful study was made are much higher than we have found in any other condition, although in neither of them was there any acute blood crisis during the time of observation. The quantity in the urine was not very great, but in two other cases from whom the stools could not be obtained for examination, very large amounts were found, corresponding to 4895 and 16,800 dilutions.

That the increase of urobilin in the urine is in the main due to an overburdening of the liver with an excessive amount of urobilin absorbed from the intestinal tract, and not to a primary functional deficiency of the liver is most probable.

The marked increase of urobilin in the stools is of special interest as evidence of a distinction between those forms of anemia associated with a great increase in hemoglobin metabolism, such as the cases of pernicious anemia we have cited and others, such as the secondary anemias following hemorrhage and carcinoma, in which the low urobilin content of the stools indicates a diminished destruction of hemoglobin.

Secondary Anemia. It is especially in cases of secondary anemia that combined urobilin estimations in the urine and stools ought to afford interesting and valuable results.

The case of secondary anemia from hemorrhage which is given above affords a striking contrast when compared with the cases of pernicious anemia. Other cases in which secondary anemia was a complication of some other condition, such as carcinoma, showed a diminution rather than an increase in total urobilin excretion.

On the other hand, the case of H. D., who had a diplostreptococcal endocarditis may be cited as an example of an anemia due to increased blood destruction. During the first twenty-six days, the average excretion in the stools was 12,841, twice as great as the normal average, and there was a dilution value of 781 in the urine. During the next seventeen days there was a fall in the stool excretion to 7801 and in the urine to 659, although there was no increase in the percentage of hemoglobin or red-blood cells. The estimation of red-blood cells and hemoglobin can give no adequate guide as to the total turn-over of hemoglobin in the body, but an approximation to this may be obtained by urobilin determinations in the urine and stools. In cases of anemia of unknown origin, the finding of an increased urobilin excretion might be of diagnostic importance in directing attention to the search for some active blood-destroying agent as the cause.

Polycythemia. The case of primary polycythemia gave very unexpected results. The urobilin in the stools was low instead of being increased, and at the same time there was a very considerable amount of urobilin in the urine, although there was no evidence of any liver disturbance. The finding of urobilin in the urine of the patient with secondary polycythemia was also unexpected.

Both these patients were markedly and constantly cyanosed, and when the connection between cyanosis and the presence of urobilin in the serum is recalled, the question arises as to whether, under normal conditions, a part of the urobilin absorbed from the intestine may not escape the liver and be changed in the blood, except under certain conditions, such as a diminution in the percentage of oxygen, when it might be excreted in the urine.

Unfortunately, we have not had an opportunity of following up this point in other cases with cyanosis.

11. MISCELLANEOUS CASES

In a large number of patients with various disorders, no pathological increase in the urobilin in the urine was found.

However, in some who showed no evidence of gross anatomical disease of the liver or of great blood destruction, considerable amounts of urobilin were present in the urine. One of these, a case of alcoholism, is of interest.

The patient was fifty-nine years old and had suffered from attacks of acute gout for forty years. There were large urate deposits around the joints. At the time of observation he was recovering from a prolonged spell of drinking, and was in a condition of great prostration with complete anorexia and vomiting. There was some edema in the legs. No liver or splenic enlargement. A few months later he died suddenly, but the cause of death was not ascertained.

Unfortunately, satisfactory collections of the stools could not be made, but the amount of urobilin appeared to be very low. One day no urobilin could be detected and on two others amounts of 216 and 1728 were found.

The urine over a period of nine days showed a daily average of 1292.

In the absence of any indication of gross liver disease, the most probable interpretation of the appearance of the large amounts of urobilin in the urine in this case is to be found in damage to the functional efficiency of the liver by excessive amounts of alcohol.

In a patient with a huge retroperitoneal sarcoma who was cachectic and feverish, the average urobilin excretion in the urine was 1545 and 11,893 in the stools. A case of carcinoma of the stomach without any metastases in the liver had an amount in the urine corresponding to 794 and 4576 in the stools.

These cases are more difficult to interpret than two others in which there were very large masses of cancerous tissue in the liver, in both of which urobilin was found in great excess in the urine.

The patient with cardiac decompensation with swollen liver, which we mentioned in our first paper, had an average of 2682 in the urine and 8619 in the stools.

Three cases of effusion of blood into the tissues were examined,

but cannot be said to throw any light on the question as to whether urobilin in the urine may have its origin in the breaking down of hemoglobin outside the vessels. One was a case of lymphatic leukemia with hemorrhages into the pharynx, gums, and orbital cavities. There was no urobilin in the urine and only 2792 in the stools.

A case of caseous tuberculous peritonitis, with a large amount of blood in the peritoneal cavity, had an average urinary excretion of 1264, and in a large pulmonary hemorrhage in a case of compensated mitral stenosis there was an average of 415 in the urine and 15,106 in the stools. There are too many other possibilities which might account for the urobilin in the urine in the two cases in which it was present. Cases of complete occlusion of the common duct with large hemorrhages are the only ones by which it is possible to decide this point.

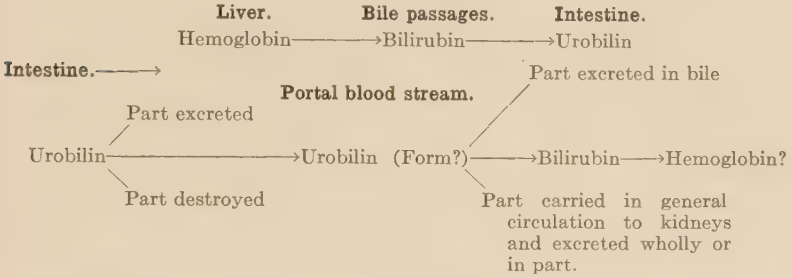
A disturbance of liver function is, of course, a possibility which is difficult to exclude in almost any case, but it does not seem justifiable at present to attribute every case of excessive excretion of urobilin in the urine without increase in the stools, to this cause alone.

12. CONCLUSIONS

A. General. 1. The intestinal formation of urobilin from the decomposition of bile frequent within the bowel is the usual mode of origin. In complete closure of the common duct due to carcinoma, for instance, there is usually absence of urobilin from the urine, bile, and stools.

2. There is evidence that the diseased liver may originate urobilin either directly as a product of its cells, or indirectly from decomposition of bilirubin within the bile passages. Thus, patients in whom no bile is reaching the intestine, may nevertheless show urobilin in large amount in the bile and to some extent even in the urine and stools if the liver itself is diseased or functionally deficient. The urobilin in the urine and stools of such cases must be due to excretion from the blood of urobilin absorbed from the liver.

The usual sequence in hemoglobin metabolism may be represented schematically as follows:



On this hypothesis, bilirubin is broken down to urobilin in the intestine and the absorbed urobilin is synthetized in the liver to bilirubin and perhaps by a reverse action again to hemoglobin.

Under abnormal conditions in the liver, formation of bilirubin from the absorbed urobilin from the intestine may fail, and further there may be a reduction of bilirubin to urobilin in the liver itself, a reversal of the normal process.

Under these circumstances the accumulated urobilin in the liver will be absorbed by the blood stream and excreted in the urine.

3. An increased quantity of urobilin in the stools indicates increased blood destruction.

In such cases, urobilin may appear in excessive amount in the urine apart from any obvious disease of the liver, because the quantity of urobilin carried to the liver from the intestine being so much increased, the fraction carried past the liver into the general circulation and so to the kidneys is sufficient to lead to an obvious urobilinuria.

4. There is a close association between increase of urobilin in the urine and disturbance of liver function. But even if increased blood destruction is excluded by urobilin estimations in the stools, it is not at present possible to regard the amount of urobilin in the urine as an approximate guide to the functional efficiency of the liver. The occasional occurrence of large amounts of urobilin in the urine of patients in whom there is no reason to suspect damage to the liver, the great and irregular fluctuations of urobilin excre-

tion in cases of liver disease from hour to hour and from day to day, and the want of knowledge as to the fate of urobilin in the blood and tissues, make it necessary to recognize that there may be other factors besides the condition of the liver and the amount of blood destruction, which influence the excretion of urobilin in the urine.

B. Clinical. Before discussing the clinical importance of the phenomena of urobilin elimination, we should like to draw particular attention (1) to the insufficiency of our present quantitative methods of urobilin estimation, especially in the urine, and to state that they undoubtedly will be very difficult to overcome because of the marked instability of the group of substances included under this name; (2) to the value, until now insufficiently appreciated, of estimations of urobilin in the stools as a guide to the amount of blood destruction in the body.

The interpretation of urobilin findings in the urine is interesting but at present somewhat problematical, whereas the determination of an increased intestinal excretion rests on a much firmer basis, and should yield results of diagnostic importance.

Since this work was undertaken with the primary object of finding out just how much significance should be attached to the presence of abnormal quantities of urobilin and urobilinogen in the excretions in ordinary clinical work, we will summarize briefly our conclusions, basing them upon our own experimental studies, clinical observations, and a fairly exhaustive study of the literature. The difficulty of the problem has been to form a judgment as to how far one is able clinically to make assertions from the data at present obtainable. To choose the essential facts from the maze of non-essential detail and from the numerous observations made to substantiate previously accepted theories has been difficult. Nevertheless, we feel that we are within safe limits in the following conclusions as to the significance of the presence of abnormal quantities of urobilin in certain pathological conditions.

(*a*) *Hepatic Cirrhosis.* Urobilinuria is of marked value as evidence of a definite pathological change in the enlarged liver of alcoholic individuals and occurs almost constantly in the hypertrophic stage of hepatic cirrhosis. In our cases, we did not find

any increase of urobilin in the stools. While in advanced cases, part of the urobilin in the urine may be derived from the formation of urobilin from bilirubin in the liver, it is probable that, as a rule, it is due to failure on the part of the liver to synthetize into bilirubin, the urobilin brought to it from the intestine.

(*b*) *Hepatic Stasis.* Estimations of urobilin in the urine are of value in judging the amount of damage done to the liver parenchyma by chronic passive congestion. Hence, a marked increase is of ominous prognostic significance in cardiac decompensation.

(*c*) *Jaundice.* Urobilinuria is absent or insignificant in cases of obstructive jaundice. Its intermittent occurrence points to an incomplete obstruction with concomitant damage to the liver. It is present in the icterus of cases with increased destruction of the red-blood cells. Careful studies for urobilin should be made in suspected cases of chloroform poisoning, acute yellow atrophy and other similar conditions in which the liver is apt to be damaged.

(*d*) *Malaria.* The great increase of urobilin in the stools and the urobilinuria which occurs in severe cases of malaria is of diagnostic importance in obscure febrile conditions. The persistence of urobilinuria after malarial attacks when there is no fever and no increase of urobilin in the stools can be taken as evidence of some complication such as hepatic cirrhosis or abscess.

(*e*) *Anemias.* By means of urobilin estimations in the stools and urine, those forms of anemia associated with an increased blood destruction may be differentiated. It is probably in this field that the most valuable clinical results will be obtained. The contrast between the very large total urobilin elimination in our cases of pernicious anemia as compared with the small amount found in secondary anemias following hemorrhage or carcinoma was very striking.

Pneumonia. A slight increase of urobilin with additional amounts at the time of resolution does not indicate a severe damage of the liver parenchyma in this disease. It is probably due to a clogging of the liver with the products of resolution and absorbed hemoglobin from the affected lung. A study of the curve of this elimination may be of value in certain pneumonias. Allowances must always be made for other factors, such as constipation, diar-

rhea, and the inability of the kidney to eliminate urobilin readily in the presence of a complicating severe nephritis. The early appearance of large quantities of urobilin in the urine in pneumonia, particularly in the presence of jaundice, makes the prognosis grave. The occurrence of urobilin in the serum of pneumonia patients is of the gravest prognostic significance. It is recognized apparently by our present methods only in the presence of a degree of cyanosis markedly unfavorable to the life of the individual.

Carcinoma. Except in those cases in which there is practically a complete disappearance of urobilin from the excretions due to an obstruction of the common duct from carcinoma, we have not found its estimation in carcinomatous cases to be of evident clinical value.

Infections. In infectious processes causing parenchymatous changes in the liver or accompanied by hemolysis, urobilin estimations are of definite value in estimating both of these factors in any given case. There is apparently an approximation between the urobilin excretion in the urine and feces and the amount of blood destruction. In such infectious processes as amebic colitis, the appearance and constant presence of urobilin may be of marked value in indicating the presence of inflammatory liver conditions, particularly abscess.

Scarlet Fever, Measles. The majority of measles cases present urobilinuria in excess, but as might be expected, the amount is less and the duration shorter than in scarlet fever, with its more definite damage to the hepatic cells.

Decompensation. As indicated previously, marked urobilinuria is indicative of pathological change in the liver in the stasis of decompensation. This circulatory stasis calls for the use of increasing amounts of hemoglobin within the body and is associated with a greater production and elimination of bilirubin, leading to an inability on the part of the overburdened and congested liver to modify the abnormal amounts of urobilin reaching it. A return of compensation is often indicated by the disappearance of a qualitative urobilinogen or urobilin test. Decompensations in markedly anemic individuals are not so apt to be accompanied by increased amounts of urobilin until very profound stasis occurs.

Nephritis. Severe nephritis of various types, even in the presence of increased production of urobilin, may prevent definite urobilinuria. Large amounts of urobilin in the urine may be taken as indirect evidence of a certain degree of efficiency in the renal epithelium.

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A DISCUSSION OF THE MANNER IN WHICH CEREBRAL MALARIA IS PRODUCED

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(By invitation)

Recent successful cultivation of malarial plasmodia *in vitro* permits experiments which indicate the exact manner in which cerebral malaria is produced. With this information at hand certain ideas bearing on the treatment of this particular clinical manifestation of the disease are suggested.

Cerebral, or comatose malaria occurs practically only in estivo-autumnal infection. As the estivo-autumnal parasite develops (*in vitro* and *in vivo*) in the red cell it is a more or less round or oval mass of protoplasm at all times after it has passed the ring stage. We have a mass of protoplasm, the parasite, developing in another mass of protoplasm, the red cell. The consistency of red cell substance is quite yielding and practically fluid. In fact red cell protoplasm is almost as fluid as the plasma in which the cells are suspended. One must stop, think, and observe before he can fully appreciate the great fluidity of red cell protoplasm. Some idea is obtained by watching the flowing and great changes in shape which occur in the red cells when pressure is made on the cover-glass of a cover-glass slide preparation of fresh blood. A still more correct impression is obtained by watching under the microscope the circulation of blood through living tissues such as the omentum or web of the foot of small animals. Red cells are seen to mould, elongate, and change in shape extensively in order to pass through narrow openings or around obstructions in the capillaries. This is particularly noticeable where red cells strike against nuclei of the endothelial cells which make up the capillaries. These nuclei project into the lumen of the capillary to a greater or less extent, and where two nuclei happen to be situated just

opposite each other the size of the lumen of the capillary is much reduced. When the flowing red cells reach such narrow places they elongate, becoming at the same time thinner and readily pass through.

The consistency of the estivo-autumnal plasmodia, on the other hand, is very firm and comparatively unyielding. Consequently whenever they attain sufficient size they cannot be moulded to pass through narrow places in the capillaries; therefore they lodge. The firm consistency of plasmodia can be demonstrated by placing a proper amount of a suspension of half-grown to full-grown estivo-autumnal parasites mixed with some red cells on a slide and covering with a cover-glass. Focus on this with a microscope and, while watching the field, make intermittent pressure on the cover-glass. It will be noted that the red cells flow back and forth as the pressure is increased or decreased. The parasites, on the other hand, do not move but remain stationary and are firmly held between the slide and cover-glass. Such a result could not obtain if the parasite was not thicker and less yielding than red cells. This idea is more forcibly impressed perhaps by injecting a suspension of large estivo-autumnal parasites, mixed with blood, into the circulation of a small animal, while watching under the microscope the circulation in the omentum or web of the foot. A parasite is carried along until it reaches a narrow place in a capillary. Here it lodges and remains and red cells pack up against it. The capillary is plugged and circulation through this particular capillary is interrupted. When such an obstruction of a sufficient number of the capillaries of the brain occurs great reduction in the amount of blood that passes through the brain results and naturally coma fol ows, just as it does when anemia of the brain is produced in any other manner. There is a tendency for the parasites to lodge in the capillaries of those organs most plentifully supplied with capillaries, such for instance as the spleen, and brain, because the large number of collateral capillaries contribute to very much lower pressure in the individual capillaries when they become obstructed. The lodged parasites continue to develop and in due course of time segment. A comparatively small number of the merozoites succeed in passing directly into other red cells which

have been pressed against the cells containing the segmenting parasites. This must be accomplished without the merozoites being exposed to the blood plasma, since we have repeatedly demonstrated that malarial plasmodia that are not protected by a red cell capsule are destroyed almost immediately when exposed to serum or plasma.

Tertian and quartan plasmodia are more yielding in consistency and capable of ameboid movement until they reach the segmenting stage. They pass through capillaries by yielding their shape to accommodate themselves to narrow places just as leukocytes and red cells do. All ages of these parasites may therefore be found in the circulating blood. It is true that most of the rosettes lodge, but they remain only a short time and comparatively only a small number of capillaries are obstructed. This explains the fact that cerebral or comatose malaria seldom or never results from tertian or quartan infection. Round or oval gametes of all the species are soft, yielding, and show more or less ameboid movement. Crescents are small enough to pass endways through the narrow places in capillaries. For this reason they may be found in the circulating blood whenever they exist. It will be seen from the above description of the manner in which cerebral or comatose malaria is produced that there is a time when the parasites causing this particular clinical manifestation would not be reached by quinine in the blood. No matter what amount of quinine is given it does not relieve the coma until the parasites causing it have segmented. It is therefore useless to continue to give such patient enormous and, in fact, destructive quantities of quinine. My own opinion is that quinine at the rate of thirty grains a day always kills all schizonts in the circulating blood and that larger quantities probably have no place in medicine. It is quite possible that many patients with cerebral malaria are actually killed by the large quantities of quinine often administered to them.

Finally it is suggested that comatose malaria may sometimes be benefited or relieved by amyl nitrite (or other nitrites) in addition to quinine. Theoretically it would have the effect of dilating the capillaries and thereby dislodging many of the lodged parasites.

BLEEDING IN TYPHOID FEVER

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It is generally recognized that the occurrence of hemorrhage in the course of typhoid fever is a serious matter, especially when it appears late in the disease. The degree of seriousness of this complication, however, has been very differently estimated by different writers, and one finds Trousseau and Graves constantly quoted as declaring that it was not an unfavorable event, and sometimes even of advantage, while Murchison, Dieulafoy, and others would have us believe that it is of extremely bad omen and never even of transient benefit. Thus, on the one hand, Liebermeister[5] writes: "If at the end of the third or fourth week a large intestinal hemorrhage appears, it may occur that the marked fall of temperature with it will have a favorable influence upon the enteric phenomena present, recovery steadily advancing from that time on. These are the cases that have led competent observers (Graves, Trousseau) to maintain that intestinal hemorrhages are by no means unfavorable in enteric fever, but are rather of favorable prognostic import." On the other hand Murchison wrote: "Although I have seen patients recover after a profuse hemorrhage, I have never seen the slightest benefit from it."[1]

It is admitted by every writer that the temperature often tends to fall after a hemorrhage, but most state that along with this lessening in the temperature there is a rise in the rate of the pulse. Thus, for example, Curschmann[6] says: "In those cases in which the patient does not die during the first copious hemorrhage, the clinical picture becomes alarmingly altered. The skin acquires a waxy pallor, there is relaxation of the features, the pulse becomes

small, and shows greatly increased frequency, lividity, and coldness of the extremities, and possibly syncope appear. With the rapid increase in the pulse frequency there is generally associated a rapid reduction in the bodily temperature. The curve may be observed to decline from 40° or 41° C. to far below the normal, that is, to 35° C. and below in a few hours. This characteristic intersection of the pulse and temperature curves is of grave prognosis." He adds later that "Quite rarely I have seen the pulse frequency fall parallel with the temperature curve, a condition that is without doubt to be considered as a favorable prognostic sign." Again, T. McCrae,[7] in speaking of hemorrhage in typhoid fever, says: "The temperature usually falls and the drop may be as much as 10° and to below normal. Still even a sharp hemorrhage may have no effect on the temperature. The pulse-rate rises, and with it the quality alters. At first somewhat bounding, later it becomes small and somewhat running." He also says later: "The results of hemorrhage are very various and there is no doubt that some patients do seem to be benefited. These are usually robust and not very toxic. The temperature curve may be lower, the pulse not increased in rate or even decreased, and the whole character of the attack milder." One can easily realize that if the hemorrhage be profuse a state of shock will ensue, with a marked fall in the temperature curve and rise in the rate of the pulse along with all the other signs of an acute and profound anemia; but the rule seems to be, certainly in our series, that the temperature and pulse curves fall together, with, as will be shown, a frequent improvement in the general condition of the sufferer.

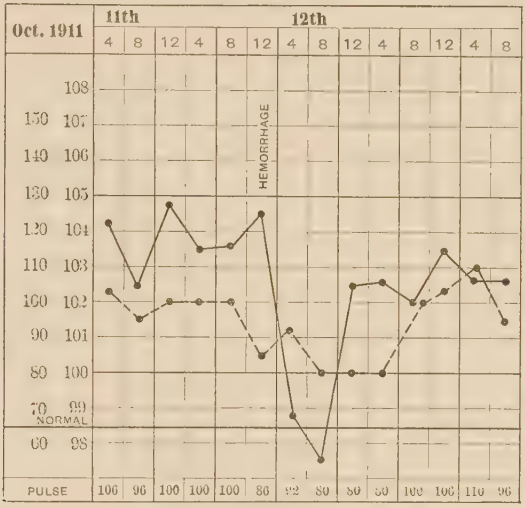
It is difficult to believe that such keen observers as Trousseau and Graves could have meant that bleeding in typhoid fever was not a serious thing, and probably Fagge was right when he wrote[3] that "Probably the real basis of their opinion was the fact that a good many patients recover from it, or, in other words, that it was not so often directly fatal as might have been anticipated." Certainly any statistical study of the disease makes it evident that the cases which have had hemorrhages have a much higher death rate than have others not so complicated. Thus in studying the last 1591 cases of typhoid fever treated in the Toronto General

Hospital it appears that the mortality was 8.67 per cent. over all, but that the death-rate among those reported as having had one or more hemorrhages was 37 per cent. This latter figure is almost the same as occurred in Curschmann's series at Leipsic, which was 38 per cent.,[6] while in Strümpell's 45 cases of hemorrhage in typhoid fever it was 42.2 per cent. In our series, if we exclude the 127 cases that had bleeding, we find that the mortality of the remaining 1464 cases was only 6.3 per cent.

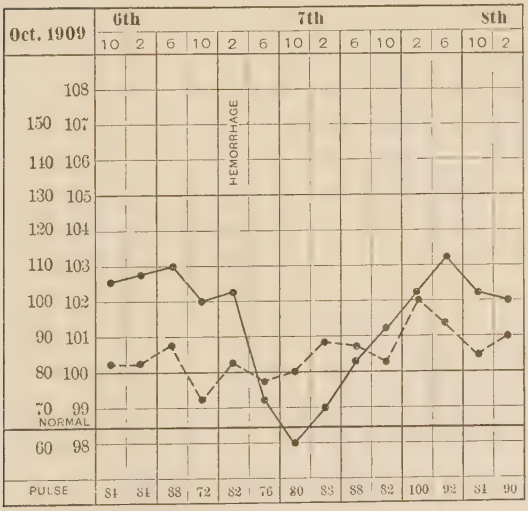
The question here naturally arises as to why enteric fever complicated with hemorrhage should have so much higher a death-rate. The ill-effects of bleeding may be due (1) to the actual loss of blood, which may be directly fatal (as it was in 8 out of Strümpell's 19 deaths in typhoid complicated with hemorrhage), or the anemia may so weaken the patient as to lay him open to other complications; or (2) the bleeding may herald perforation and also is usually significant of a severe infection. If it were not for these two classes of dangers which are more or less imminent in hemorrhage cases, the loss of blood, if of moderate amount, might be welcome. Many writers, for example Liebermeister and McCrae, not to mention Trousseau and Graves, have remarked how often patients seem to improve after moderate hemorrhages, and if it were not for the dangers looming up of the bleeding becoming uncontrollable or being a precursor of perforation, probably most physicians would be pleased rather than otherwise with the at least temporary benefit which so often accrues.

The appended twelve charts are taken from among the cases of intestinal hemorrhage (with one exception where the bleeding was through venesection) that occurred in our series at the Toronto General Hospital, and they show how the bleeding was followed by a more or less marked fall not only in the temperature but also in the pulse-rate. They are perhaps the best examples, but most of the other 115 charts showed more or less of the same thing. They do not, of course, show the improvement in the general condition that was so often noted, but a perusal of the epitomes of the histories will make this evident. The notes of progress are exactly as they were made at the time by members of the staff and the house physicians. It will be noted that the improvement

in the temperature and pulse curves, while often very transient, in some cases may last for days and may even usher in convalescence. It is impossible in the face of such evidence to agree with

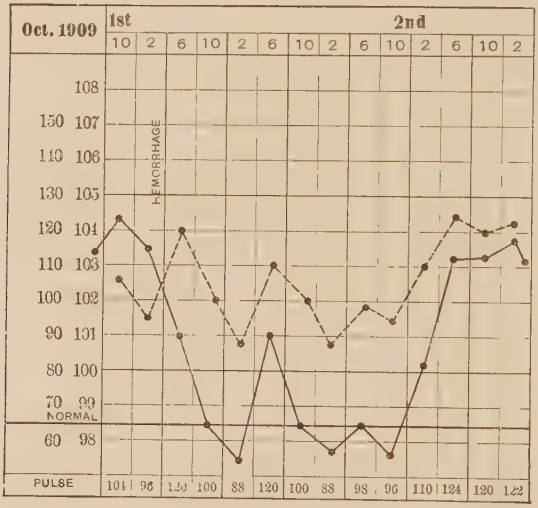


Case I

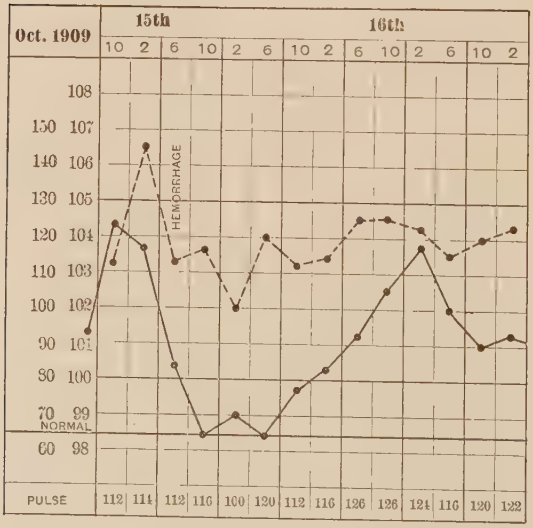


Case II

Fagge, when he says: "According to Liebermeister, hemorrhages also diminish the pulse and are often attended by a marked amelio-

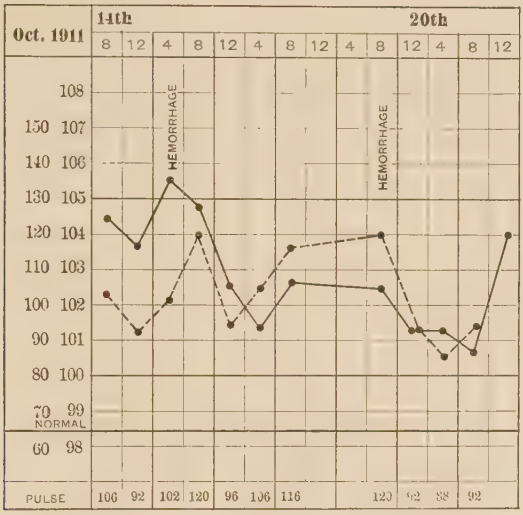


Case III

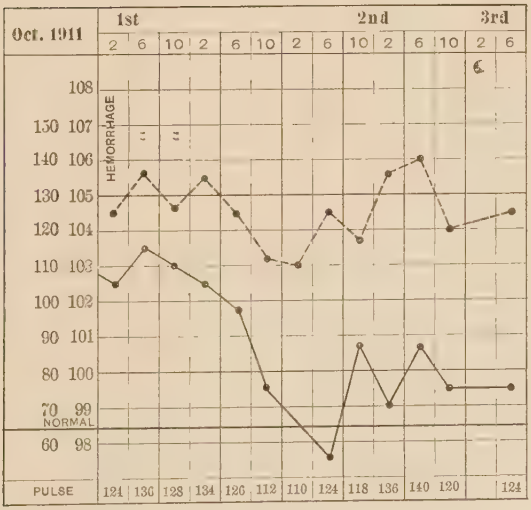


Case IV

ration of the cerebral symptoms. But all these effects are transitory, for by the end of twenty-four hours the fever is as high or

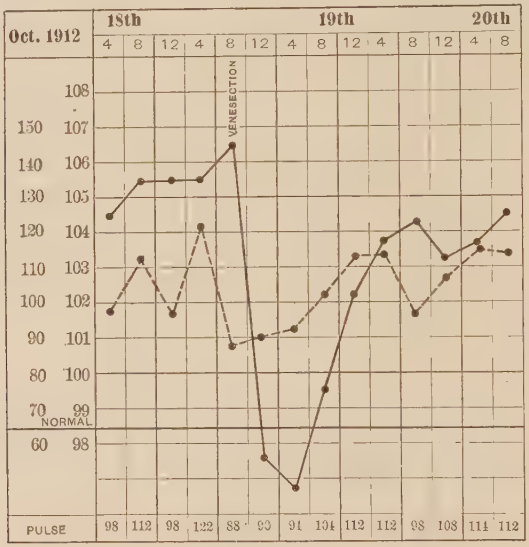


Case V

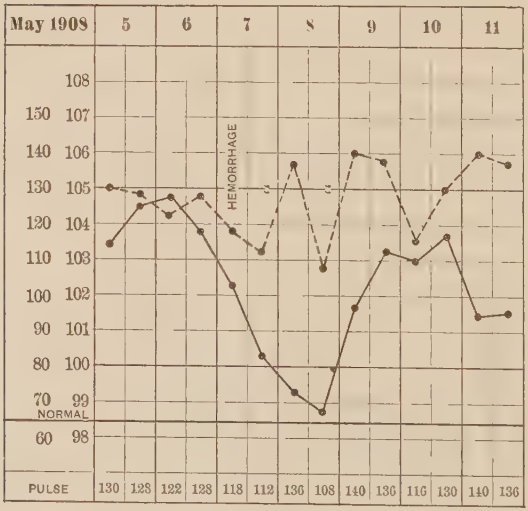


Case VI

higher than before the hemorrhage," or with Murchison who wrote: "I have seen patients recover from profuse hemorrhages. I have never seen the slighest benefit from it."

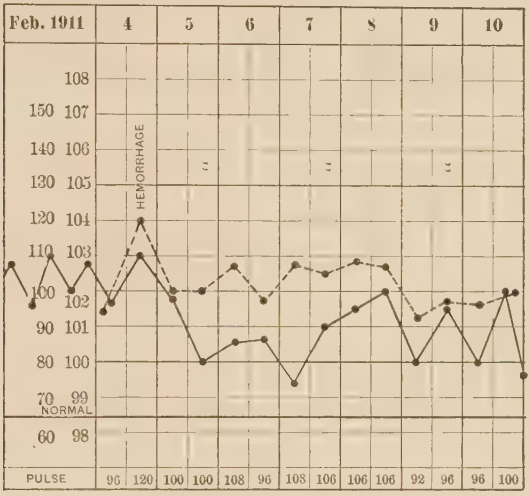


Case VII

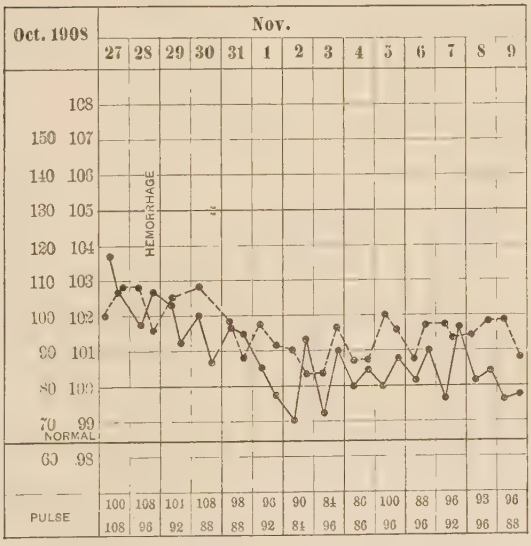


Case VIII

It is difficult to explain how the good effects that may follow a hemorrhage come about. There is no doubt, however, but that

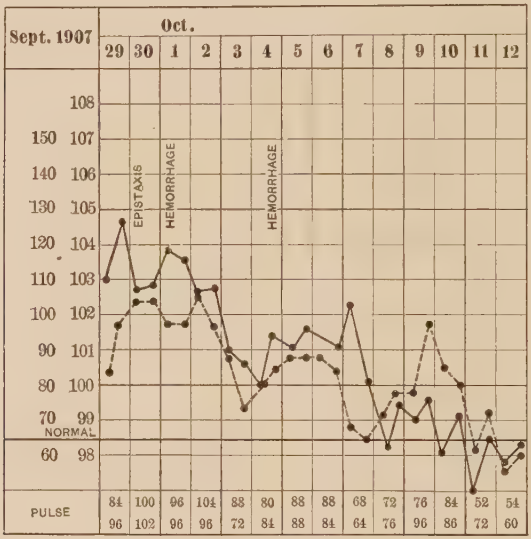


Case IX

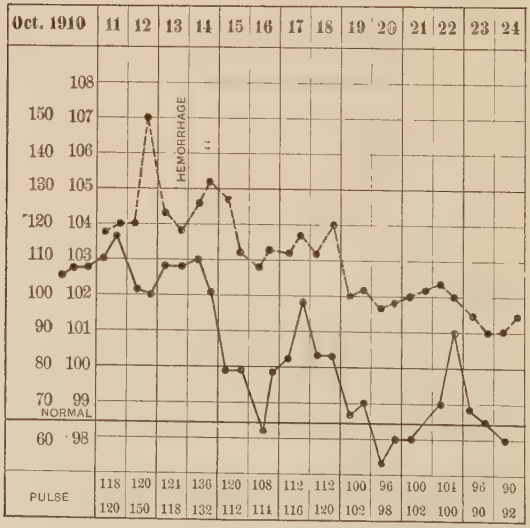


Case X

it produces a profound effect upon the whole bodily economy. Thus bleeding has been shown to bring about an increase in the



Case XI



Case XII

flow of urine,[13] to greatly increase the intake of oxygen, with proportionate raising of tissue oxidation;[9] It hastens the coagulation time of the blood more than does any other single agent with which we are acquainted.[10] Roux and Vaillard[5] showed in 1893 that it produced a rapid increase in the antibodies contained in the blood, and Dreyer and Shroeder, of Copenhagen, about four years ago, demonstrated that it increases the specific antibodies in typhoid and paratyphoid both in experimental animals and in man. H. Whitehead[12] fully confirmed this two years ago in a study of typhoid complicated by hemorrhage, in which the agglutinating power of the blood was enormously raised by the bleeding. Further, in toxic conditions such as uremia and other less-defined states, where there is high blood-pressure, bleeding appears to in some way lessen the toxemia, and possibly in typhoid it may have some similar effect.

Finally, Whitehead in his paper two years ago suggested that the good effects of hemorrhage in typhoid fever might be attained and the evil ones (associated with intestinal hemorrhage) avoided by the timely use of venesection in those cases which are not doing well on account of severe infection and toxemia, and with this suggestion I would heartily concur. Of course, in the days when venesection was considered to be a panacea for almost all ailments, cases of typhoid fever must have been bled; but it is impossible to get at any reliable data as to the results, as at that date typhoid fever was not differentiated from other cases of continued fever. Even Marshall Hall, who is considered to be the great opponent of bleeding, and who gets the credit of having brought about the almost complete abandonment of this time-honored method of treatment, states that in fevers and eruptive fevers[8] from six to fourteen ounces of blood should be removed, so it is not likely that typhoid fever escaped.

Only one case is shown in our series (Case VII) in which bloodletting was done, but the sequence of the venesection was there most marked. Theoretically, the method appears to be indicated in severe cases, and if the removal of blood by venesection be a moderate one, say of six to fourteen ounces, as was recommended by Marshall Hall, it can do no harm and may possibly be productive of great good.

Case I (Not yet filed).—Female, aged twenty-two years. Admitted October 1, 1911. Duration of illness about two weeks. Was dull and drowsy; flushed.

October 7. Vomited a great deal and is dull and very toxic.

October 12. Very dull and toxic. Vomited twice today. At 5.30 A.M. a profuse hemorrhage from bowel.

October 13. Brighter today. Pulse, 92; temperature, 98.6°; systolic blood pressure, 72; diastolic, 45.

October 19. Brighter today. Toxemia not so marked as it was. Temperature, 102.4°; pulse, 92; respiration, 22.

October 31. Quiet and sleeping well. No vomiting since October 12. She steadily improved and was discharged well on January 21, 1912.

Case II (Vol. XXXIX, Case 6088).—Male, aged thirty-five years. Admitted October 4, 1909. Duration of illness about two weeks. Was in fairly good condition. Abdomen not distended, pulse very dicrotic.

October 6. Chilly and free sweats. Lips dry. Tongue clean and very red. Later in day drowsy and had severe headache and abdominal distress.

October 7. In early morning and again just before noon patient complained of chilly feelings and sweated. Was quite restless, and had severe abdominal pain, with no rigidity or tenderness. Some nausea. Bowel movement at noon showed small amount of dark blood. Half an hour later a large amount of blood. Pulse not changed. An hour later a third hemorrhage, very large. No change in pulse until then, when it became rapid; had general faint feeling, blanched, and hands clammy, and half an hour later had profuse perspiration. At midnight pulse rate not changed and temperature 99°.

October 8. Slight hemorrhage at 9 A.M. This recurred slightly for two days. Pulse rate not altered for the worse.

October 11. General condition satisfactory. Temperature now running at a satisfactory height.

November 13. Uninterrupted progress. Soon after left the hospital well.

Case III (Vol. XLVII, Case 6917).—Female, aged twenty-eight years. Admitted September 19, 1909. Duration of illness about one month. Fairly severe attack.

September 26. Very drowsy and slept most of day. Tongue drying. Some diarrhea. Abdomen distending.

September 29. Abdomen distention marked. Pulse dicrotic. Patient very dull.

October 1. Hemorrhage occurred in night and today several times. Pallid. Skin cold and clammy. Pulse poor quality. Respiration sighing.

October 2. No more hemorrhage. Patient brighter.

October 4. Abdomen distended. Respiration sighing. Pallor marked but pulse unchanged. Resting well at night.

October 5. Slight hemorrhage today. This patient eventually left the hospital well.

Case IV (Vol. XLVII, Case 6926).—Male, aged thirty years. Admitted September 30, 1909. Duration five days. Severe case with high fever, easily lowered always by three grains of aspirin.

October 14. Restless night, trying to get out of bed and talking to himself. Subsultus marked. This morning sweating very freely. Very drowsy but rational until tonight when he has been sitting up in bed and trying to get out of it. 8 P.M. pulse, 120; respiration, 20; temperature, 105°. 10 P.M. pulse, 104; respiration, 20; temperature, 100.2°. Pulse and abdomen good.

October 15. Profuse hemorrhage at 6 A.M., bright red. Pulse irregular and intermittent, very small and thready. Profuse sweating. 8 A.M. pulse, 144; respiration, 32; temperature, 103.2°. At noon patient quite bright, pulse, 112; respiration, 24; temperature, 100.2°. At 4 P.M. pulse, 116; respiration, 28; temperature, 98.2°. At 8 P.M. pulse, 120; respiration, 20; temperature, 99°. Pulse of better quality. Another hemorrhage in evening. Midnight, pulse, 120; respiration, 20; temperature, 88.3°.

October 16. Noon. Pulse, 120; respiration, 24; temperature, 101.1°. Patient brighter. Pulse of better quality than this morning. Patient has been very quiet and sleeping most of day. Abdomen and pulse satisfactory. After this the patient had several hemorrhages at intervals of several days. Each one was followed by a temporary drop in the condition. He eventually completely recovered.

Case V (Vol. LXXIV, Case 9772).—Male, aged twenty-six years. Admitted October 9, 1911. Duration of illness ten days. Dull and heavy and covered with rose spots. Lips dry. Temperature, 104.8°.

October 14. Very dull and heavy. Perspiring freely. Respiration, 36; Pulse, 105. Had a free hemorrhage this morning.

October 15. Patient appears to be improved; less toxic; tongue still very dry.

October 16. Pale and hard to rouse. This morning had two hemorrhages. Has twitching of eye-brows and mouth. Tongue very dry.

October 17. Brighter and better in every way.

After this he steadily improved and left the hospital well on December 21.

Case VI (Vol. LXXIV, Case 9773).—Female, aged fourteen years. Admitted September 13, 1911. Duration of illness about twenty-six days.

Very ill on admission. Tongue pale and moist and covered with white fur. Abdomen distended. Remained very ill and toxic during the next few days.

September 30. Restless night. Temperature, 103° to 104°. Pulse, 124 to 134. No marked abdominal distention. At 11 P.M., had rather profuse hemorrhage and again next day.

October 2. Abdomen distended. Involuntary urine. Later became worse and more toxic with filling up of bases of lungs and died on fifth instant.

Case VII (Not yet filed).—Female, aged thirty-four years. Admitted October 17, 1912. Duration of illness two weeks. Very toxic and pays no attention to what is going on. Lips dry and cracked. Tongue reddish brown. Spasmodic movement of chin. Hands are tremulous. Abdomen distended and tympanitic. Spleen and liver both palpable.

October 18. About the same. Seems dazed and at times picks at bedclothes. Temperature, 105°; pulse, 110. This evening five ounces of blood were drawn off from median-basilic vein of left arm and ten ounces of normal saline solution was injected into vein. 6 P.M., temperature, 106°; pulse, 130. Whisky half an ounce every four hours. Cold colon douche. Ice pack. Caffeine, 1 grain; aspirin, 2 grains, and acetanilide, $\frac{1}{4}$ grain. Repeat in half an hour, and again in two hours if temperature not lower.

October 19. 9 A.M., temperature, 99°; pulse, 88. Is listless and weak. Mutters at times. Tongue dry and reddish brown. Lips dry. After this continued very ill but less desperately so, and by the end of the month was much better and left the hospital well before the end of the year.

Case VIII (Vol. XXV, Case 4210).—Female aged thirty-two years. Admitted April 28, 1908. Duration ten days. Was very ill on admission.

May 1. Temperature high. Delirious and weak.

May 7. Hemorrhages early this morning and again at 1 P.M. Blood very dark and not in large quantity. Abdomen much distended.

May 8. Another hemorrhage (slight) at 11.30 last night. Distention still marked. A free hemorrhage at 6.15 tonight. Pulse much as before.

May 10. Pulse very weak. Restless and unconscious most of the time.

May 13. Marked improvement in last two days.

May 19. Weaker and died at 5.15 A.M.

Case IX (Vol. LXIII, Case 8870). Male, aged thirty-one years. Admitted January 19, 1911. Duration of illness about nine days. Fairly well on admission. Was evidently near the end of the attack. Temperature 100°, and was soon normal. A week later had a relapse and on February 4 a hemorrhage. On day before was dull and sleepy. Systolic blood-pressure 110. Slight bloating. Lips crusted and tongue red and beefy. Had another hemorrhage on February 5, again on February 7 and 9. After that patient steadily improved and left the hospital well, on March 25.

Case X (Vol. XXXI, Case 5145).—Male, aged twenty-two years. Admitted October 22, 1908. Been ill for two weeks. Weak, sleepy, delirious and hard to rouse. Hemorrhage on October 28 and again on October 30.

November 1. Not so delirous and taking nourishment well.

November 4. Able to speak.

Recovered without further complications.

Case XI (Vol. XVIII, Case 3302).—Male, aged twenty-two years. Admitted September 23, 1907. Had been ill for three weeks when admitted; now feeling better. Pulse showed marked dicrotism.

September 30. Epistaxis; feeling better.

October 1. Slight hemorrhage from bowel. Pulse and temperature not affected by it.

October 4 Another slight hemorrhage.

October 5. Systolic blood pressure, 120.

October 10. Another epistaxis. Is feeling well.

November 2. Discharged well.

Case XII (Vol. LXIII, Case 8791).—Male, aged twenty-four years. Admitted September 19, 1910. Been ill for four weeks. Now very ill and drowsy. Pallid. Tongue dry and coated.

October 11. Nervous and trembling. Very toxic. Involuntary evacuations. He looks almost moribund. Drowsy and stupid. Lungs show a consolidation at right base. Is extremely ill.

October 13. Still very low. Profuse hemorrhage today.

October 14. More clots in stools.

October 15. Much better today. Lung condition clearing. Pulse, 106 to 122; temperature, 98.2° to 99.2°. Had a good day but did not rest so well last night.

November 3. Doing well. Temperature and pulse normal.

Was discharged well on November 27.

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DENTAL SEPSIS: ITS RELATION TO THE SYSTEM

By C. N. B. CAMAC, M.D.
NEW YORK CITY

The cases upon which the following observations are based presented purulent infection in and about the teeth. The terms used in literature to indicate this condition are oral sepsis, Rigg's disease, pyorrhea alveolaris, dental sepsis, dental abscess, necrosis, etc. By the internist these terms are very loosely used, and one must turn to works upon dentistry to get any accurate information of the nature and extent of the *local* process. Even in such works, however, there is no adequate explanation of the relation of these variously situated foci to each other. Works on internal medicine have as yet no comprehensive consideration of this subject and its causitive relation to some of the most destructive systemic processes (arthritis, endocarditis, etc.), a relationship which we know to be of primary importance in the consideration of the etiology, diagnosis and therapeutics of these conditions. It is the duty of the internist to familiarize himself with this focus of pyogenic infection *in its early stage* and to coöperate with the dentist as with the surgeon in the eradication of foci of pus in any part of the body. The teeth, especially at the pulp, may, like the tonsillar, peritonsillar, and deep urethral tissues, harbor pyogenic organisms and even small amounts of virulent pus without local manifestations, although systemic manifestations having apparently no relation to this source appear from time to time, and may reach a crippling or fatal degree. It is this latent or subtle quality in the local infection which causes it to be frequently overlooked or discounted by the internist. Such foci can often be detected by radiographic examination only. In one instance (Case I) the

only manifestation was a slight crepitation of the left temporomaxillary joint, which was unaccompanied by pain or tenderness. There was slight ear pain for which the patient consulted an aurist. This, and the unusual sound in opening and closing the jaw, was the only complaint. The radiograph showed a pulp abscess. The tooth was removed and a pure culture of Streptococcus viridans was obtained from the pulp, socket and gum, and the blood gave positive complement fixation for the same organism. There was no fever at any time and no leukocytosis. Vaccines were prepared from this tooth but were not used at the time as conditions did not seem to justify doing so. A few months later general arthritis developed and the autogenous vaccine was immediately employed, with marked benefit but not with entire disappearance of the arthritic manifestations. The blood still showed positive fixation for the same organism. On further search another tooth was found with small pus focus, and on removal of this there was rapid improvement, with ultimate disappearance of the arthritis. The manifestations of arthritis were pain on motion, active and passive, and slight tenderness on deep palpation, but no redness or local fever. The knees, ankles, wrists, elbows, and small joints of the hand were involved. The temporomaxillary joint was, however, the only one permanently damaged, and in consequence the crepitation persists. (See case reports, Case I.) This case well illustrates the slow, steady absorption with destruction, unless the focus is detected and the process checked. It is always possible in the protracted cases in which no removal of the focus or other checking of the infection is carried out, for new foci to develop in the joints or soft tissues. Under these circumstances the condition may become progressive, consequent to but independent of the original focus, and often hopelessly to the joints or visceral tissues. The persistence of the temporomaxillary joint signs in the case just cited makes it possible that here may be a new focus of infection which may appear in other localities later. Several such new foci, even though the original focus has been drastically treated by removal of the tooth and by curettement, makes the clinical problem one of great difficulty, disheartening the patient and baffling the physician. Vaccines under these

circumstances hold out the only rational therapeutic measure. This case demonstrates also the importance of close coöperation between dentist and internist. This obligation to coöperate rests as much with the dentist, if not more so, as with the internist. The dentist may find a tooth abscess with which, in most instances, he deals mechanically. Later the internist sees the same case and though he may associate the history of the diseased tooth with the systemic disturbance which he now finds, it is often impossible, at that late date, to accurately correlate the two processes. The dentist in most instances does not make cultural studies of the pus and thus the only opportunity of detecting the invading organism and of preparing vaccines, may be lost. If, as seems likely, vaccines prove to be the only certain means of combating these destructive pyogenic infections in their advanced stages, the loss of the opportunity to procure this important therapeutic agent would be a serious and culpable omission.

Setting aside the question as to whether the dental involvement is cause or effect of a general sepsis, the clinical fact remains that the material procurable from such foci frequently offers the only, and often brief, opportunity to identify the invading organism and of procuring materials from which vaccines may be made. I prefer to emphasize this feature of the subject which is of so great diagnostic and therapeutic importance, rather than that of cause and effect, which as a question of etiology, involves problems possibly unsolvable. The cases upon which this report is based have been studied in coöperation with Drs. M. I. Schamberg, Alexander Currie, W. D. Tracy, Harold S. Vaughan, dentists of New York City, three of whom are also graduates in medicine. Among the radiographs accompanying this article I have included those of case which have come under the personal observation of those dentists, through whose courtesy I am enabled to reproduce them here.

In using the term coöperation I do not mean to infer that the patients were told to consult the dentist merely, but I accompanied them to the dentist's office and studied with him the radiographs and local conditions. I believe such consultation to be as necessary as those common between surgeon and internist. When

pyogenic dental infections, requiring liberation of the pus existed, arrangements were made for bacteriological specimens to be procured at the dentist's office, and later, if conditions indicated, a specimen of blood for culture and complement-fixation tests was taken. A certain number of dentists are in accord with this practice: indeed a small number have gone beyond the medical practitioner and without his coöperation is studying cases with just such thoroughness as outlined above. There is, however, among the dentists a large class of dental tinkerers who practise upon the easy persuasibility of the public. A large mass of mechanical work is thus done upon the teeth with often an entire neglect of the destructive focus of pus. A specific instance of this occurred in Case II. In this case there were (see case reports, Case II) areas of pus from which Streptococcus viridans in pure culture was obtained. These areas of pus were detected only by the radiograph, there being but slight local symptoms or signs. Into the roof of the mouth of this patient a dentist had inserted an elliptically curved bar of metal as large as the lead of a pencil with possibly some idea of correcting a dental displacement, but with no correction of the pus focus. Subsequently this patient developed a cervical spondylitis which cleared up shortly after draining the abscess cavities. One may even go further and state that some of this mechanical work entraps pus which before such interference was draining into the mouth cavity, and thus at least lessening systemic absorption. Crown work and filling are two common pieces of mechanical work which if improperly done may be a means of thus entrapping pus. A cavity in which a small quantity of pus is allowed to remain may harbor virulent organisms which slowly extend the inflammation to the surrounding tissues, setting up large abscesses with active systemic absorption. Case IV illustrates the action of imperfect filling by producing irritation and inflammation, (see case reports, Case IV). The radiograph in this case showed a shadow which was thought to be a pus area but proved to be only thickening of the tissues. Cultures from all the suspected areas and from the root of the imperfectly filled tooth (which was drawn) were negative. There was, however, a positive fixation in the blood for three out of twelve strains of Streptococcus viridans.

Four months prior there had been an acute abscess of a tooth not connected with this imperfect filling, but severe enough to cause pain and swelling and to require radical treatment. No cultures were taken at the time of the operation but the positive fixation found later and the inflamed areas about to become purulent were significant. This case seems to fall into a group of cases of latent streptococcus infection in which faulty dental work would be a sufficient exciting cause to establish an active local process with systemic absorption. The faulty dental technique in crown, filling, and other mechanical work here referred to is well known to dentists, and it is mentioned not as an arraignment of the dental profession, but for the information of the general practitioner. It may be further stated that so far from being at fault the dentists must be given the credit of pioneer work in dealing radically with pyogenic infection in and about the teeth and in the use of radiography in detecting such conditions. Evidence of this is found in the writings of such dentists as A. Witzel,[1] L. C. Ingersoll,[2] W. J. Reese,[3] Louis Jack, C. N. Pierce,[4] and many others who published their observations between the year 1880 and 1900. While these were general considerations following the initial communication of John W. Riggs, of Hartford, Conn., which was made in October, 1875, they all showed an appreciation of the relation between these local dental conditions and systemic disturbances. The later writings of such dentists as M. I. Schamberg,[5] formerly of Philadelphia; Harold S. Vaughan,[6] of New York; Thomas L. Gilmer,[7] of Chicago; to mention a few only, show an even greater appreciation of a probable relation between oral sepsis and many serious systemic diseases, an appreciation not yet shown by the majority of general practitioners. Among medical men, William Hunter,[8] of London,

[1] Vierteljahrsschrift für Zahnheilkunde 1882; British Journal of Dental Science xxv, 153.
[2] Ohio State Journal of Dental Science, 1881, i, 189.
[3] Dental Cosmos, 1886, xxv, 550.
[4] International Journal, 1892, 1894 and 1895, vols. xiii, xv and xvi.
[5] Dental Cosmos, January, 1906. Dental Brief, June, 1906.
[6] Journal of the Allied Dental Sciences, March, 1913. (In this communication Vaughan shows the infection to be due to Vincent's bacteria without typical pus pockets.)
[7] Illinois Medical Journal, March, 1912.
[8] British Medical Journal, 1900, ii, 215.

and the late Dr. Kinnicutt,[1] of New York, have been in recent years the most active in bringing before the medical profession the importance of this subject.

There are two chief factors militating against the thorough investigation and prompt treatment of these cases.

1. The dentist and the internist, through the improved standards of dental work, are coming together more and more in consultation and coöperation. This was, however, not always the case, and recalls the relation which existed between the surgeon and physician in England in the days of Coffee House consultation in which the druggist was the middle man. The physician in these days merited his lower position in the scientific world and the surgeon justly felt that these doctor druggists were not men worthy to coöperate with. As the internist built up his diagnosis upon scientific research it became possible for the surgeon to meet with him and study the case. Such is true also of the dental profession, and in 1904 the science had reached such a degree of accuracy that a Section of Dental Surgery was established in the British Medical Association[2] in which dentist and physician participate. Throughout the country today there is developing a class of dentists whose opinions are based upon carefully weighed evidence and who are devising and carrying out operative measures as delicate in technique as some of the more important surgical operations. This first factor against the proper care of these cases can be best removed by the direct consultation between dentist and internist and their continued coöperation in the care of the case.

2. The second factor is the tenacity with which men and women alike will insist upon retaining rotten fangs in the mouth. The dentist regards the loss of a tooth as the internist does the death of a patient, and in this opinion the dentist has the insistent support of the patient. It is not an exaggeration to say that in saving certain teeth the dentist may be condemning the patient to a living death through subsequent crippling arthritic infection or actual death through septic invasion of some vital organ. This factor can best be removed by educating the public through the medium of the internist

[1] Proc. Roy. Soc. Med., April, 1913, vol. vi, Sup. No. 7, May, 1913.
[2] British Medical Journal, November 19, 1904.

and dentist, to the realization of the seriousness of these conditions. When this is correctly understood by the patient, the removal of the offending teeth will be as readily consented to as tonsillotomy, or the opening of a mastoid. Dr. Hunter[1] has dealt very thoroughly with the obligation of the dentist in this matter and his opinions are warmly supported by many of the best dentists. I believe, however, that some of his remarks may be taken with great directness by the internist who is not frequently the first under whose observation these cases come.

Report of Cases

Case I.—W. W., female, aged thirty-five years. Married. Since April, 1912, complained of pain in the left ear for which she was referred to a specialist who reported subacute inflammation of the left Eustachian tube. She was under treatment for this from time to time during the summer, but the condition not improving she consulted, of her own accord, another specialist and was told by him that he found nothing wrong with the throat, ear, or nose, and referred her back to me. October 7, 1912, patient seen again by me when the following notes were made.

Complaint. Pain and tenderness located in the left ear. Distinctly audible crepitation of the left temporomaxillary joint.

Family History. Negative, except that one brother who is now forty-five is a victim of arthritis deformans which began about nine years ago. He was acutely ill for several months and while the joint condition is not progressive he has occasional attacks of fever. He has been seen by several of the prominent consultants of this country. Of two sisters, one (also under my care) has had septic infection of an antrum, for which she was treated by a specialist. The other sister had involvement of the small joints of the hands about the same time that the brother became infected.

Past History. Presents nothing of importance except that wine is taken freely with meals and at other times also. The patient has one child. There is no history of miscarriages or pelvic infection.

Physical examination presents nothing of importance that has not already been given. The patient is slender and of nervous temperament.

Blood Examination

Hemoglobin (Fleischl)	78 per cent.
Red cells	5,200,000
White cells	7,400

[1] Practitioner, December, 1900.

Differential Count of White Cells

Polynuclear neutrophiles	78 per cent.
Transitional cells	0 "
Large mononuclear cells	1 "
Large lymphocytes	0 "
Small lymphocytes	19 "
Eosinophiles	2 "
Mast cells	0 "
	100 "

Urine examination is negative.

October 12, 1912, the patient was seen in consultation with Dr. Currie (dentist) and radiographs of the temporomaxillary joint and teeth were studied. Nothing was observed in the joint, but suspicion was directed to a tooth which it was determined to remove. In the socket and about the pulp of this tooth pus was found, cultures from which were taken by Dr. Hastings at the moment of its removal. Bacteriological report is as follows: Cultures from the tooth, the tissue, and from the tooth socket, give pure Streptococcus viridans; and cultures from pus about the gum and about the tooth give Streptococcus viridans and Staphylococcus aureus. A blood culture taken a few days later showed no bacteremia but for seven strains of streptocci, the fixation was negative for four strains, positive for three strains of Streptococcus viridans. There was no fixation for the gonococcus and the blood for lues was negative. We have, therefore, evidences of a local Streptococcus viridans abscess with systemic absorption. That the temporomaxillary involvement was a manifestation of this sepsis was a reasonable conclusion, borne out by subsequent developments. The cultures were preserved for the purpose of employing vaccines at a later date should the removal of this tooth and a cleansing of the socket not prove curative, or should other joints show evidences of infection. The patient continued under general observation with marked improvement of the ear condition. The crepitation of the temporomaxillary joint continued but without pain or tenderness. In November, 1912, the patient went West, where she remained about two weeks. During this time she experienced, for the first time, pain in the ankles, knees, and wrists. There was no swelling, redness or other local signs. On her return to New York in the latter part of November, 1912, the pain continued in the joints noted and extended to some of the finger-joints and to three toes of the right foot. The pain was worse in damp weather. This condition became sufficiently severe to alarm her, and on December 27 she reported to me. There was no fever and no local signs, except slight tenderness on

moving the larger joints and on pressing some of the smaller joints. There was pain, for the first time, in the left temporomaxillary joint. There have been no chills or sweating. The knee-jerks are present. The pupils react normally and there is no Romberg. It was decided to begin vaccine and she received her first inoculation January 9, 1913. Up to April 21, she received twenty inoculations. By March 31, except for slight pain in a toe-joint of the right foot, the joints were free of all symptoms, a condition which up to that date had existed for about three weeks. She felt better than she had at any time for several years. The details of the vaccine therapy are omitted. By April 14, 1913, patient complained of considerable tingling in the legs, swelling and puffing of the feet. There was no fever, and though she had maintained her weight and the appetite was good, she looked badly. April 21, she complained of feeling wretchedly, joints were more sensitive and she noticed puffiness of the feet especially at night. The diet and hygenic surroundings were carefully regulated and a tonic was prescribed and the vaccines were increased. She however continued to do badly. Blood showed the following:

Blood Examination

Hemoglobin	100 per cent. (Sahli corrected)
Red-blood cells	4,720,000
White-blood cells	9,000
Color index 1.	

Differential Count

Polynuclears	71.0 per cent. (300 counted)
Lymphocytes	19.6 "
Large mononuclears	5.0 "
Transitionals	3.6 "
Eosinophiles	.6 "
Red-blood cells normal	

Blood negative for organisms, but the complement-fixation was positive for the same strains of Streptococcus viridans as in the test made October, 1912.

On May 7, the teeth were again thoroughly radiographed, and though a careful study of these by two dentists and myself failed to detect pus shadows, Dr. Currie discovered a small area of pus near a devitalized tooth adjoining the seat of original infection. There was also impingement of a neighboring tooth which accounted possibly for the pain. This tooth was removed and the area thoroughly curetted, and rapid improvement followed. The local pain entirely disappeared and in two or three weeks

the joints gradually ceased to cause trouble. The general health improved, and except for occasional observations by the dentist, the case passed from medical attention. The crepitation in the left temporomaxillary joint persists and has been sufficiently marked to be audible to those sitting nearby. This joint, therefore, is probably permanently damaged.

Case II.—W. R., male, aged forty-four years, married; seen May 27, 1913, complained of pain and tenderness in the vertebral column about opposite the seventh cervical.

Past history presents nothing of importance. Has no children, and wife has had no miscarriages. Alcohol and tobacco in moderation. Gives an indefinite history of some trouble with the knee-joint which he attributes to trauma two years ago; occasionally feels slight twinges of pain in this knee on motion. Has had very slight pain at times in some of the toe-joints. Is an active business man.

Present. Vertebral trouble began about January, 1913; not progressive and not noticeable when sitting or lying still. Up to June, 1912, took recreation in boxing, but since then on account of the neck condition, has not been able to do so. At times he fears to move because of the pain. In every other particular the general health is good.

Examination. A large, well-built, healthy-looking man; dark complexioned, of American-German parentage. There is no pigmentation of the mucous membrane and the skin pigmentation is uniformly distributed. Carries his head in a fixed position, suggesting "stiff neck." On lightly tapping the top of the head tenderness is localized to about the sixth cervical vertebra, at which point the pain is localized; there is also here well-marked tenderness on pressure. A radiograph discloses no definite change at this articulation.

Blood Examination

Hemoglobin (Fleischl)	85 per cent.
Red cells	6,016,000
White cells	6,000

Differential Count

Polynuclear	62 per cent.
Large lymphocytes	4 "
Small lymphocytes	26 "
Eosinophiles	3 "
Transitional cells	5 "
	100 "

Radiographs of the teeth were studied with the dentist, Dr. Currie, and suspicion was directed to the upper right canine and the upper incisor (see Figs. 2 and 6); in addition the dentist detected discharging pus from the upper right canine. On dealing with these teeth radically, pyorrhea, with marked destruction of the alveolus of the upper right canine which was discharging, was found; also central necrosis of the right upper incisor, which, in Dr. Currie's opinion was of some duration, together with a pus pocket in the lower left molar under an imperfectly fitting crown. Cultures by Dr Mann gave Streptococcus viridans. The offending teeth were removed and all the infected areas thoroughly cleaned out. Tonic treatment was at the same time instituted. One week after this radical treatment, the condition of the neck, which had existed for five months, markedly improved, and by the end of June entirely disappeared. This case had been under the observation of a dentist who was seen for the routine care of the teeth and who entirely overlooked the purulent condition, inserting in the mouth the badly fitting crown and a bar for the correction of a suspected displacement.

Case III.—J. J., female, aged forty; married. Seen September, 1911. Pain and tenderness left knee-joint.

Past history nothing of importance. Borne two healthy children, no miscarriages. Has been in uncertain health for some years, but condition was attributed to nervousness, nothing definite manifesting itself.

Present trouble began with pain and tenderness on the outer aspect of the left knee-joint, aggravated by walking. This joint was treated locally by an orthopedist and after eight months of wearing a brace and being under general tonic treatment, baths, etc., other joints became painful, including the temporomaxillary joints, making the chewing of food and articulation difficult. One year after initial knee condition, fever, of an irregular type appeared. Eighteen months from onset an intermittent odor of the breath was noticed and this first attracted attention to the teeth which had given only such signs as were considered common and unimportant. On thorough examination of the mouth, pus was found to exude from the gum about a molar tooth which being removed disclosed a pus cavity in the gum from which was obtained a dram of pus. From this pure culture of Streptococcus viridans was obtained. The jawbone was found to be partly involved in the purulent process. The patient sustained a typhoid temperature for four months with the involvement of many of the large and small joints. Autogenous vaccine was used continuously over a period of three years. During this time phlebitis in one leg developed. For five months there has been steady improvement in the general condition but several of the joints seem permanently damaged and the knee-joints are fixed (by a possible tendon or muscle shortening) at an angle of 45°. This case will be published elsewhere in detail from the bacteriological, vaccine, and arthritis view-points. For this reason the above brief outline only is given.

Case IV.—C. S., widow, aged forty-two; complains of malaise, indigestion, and broken sleep.

The family history is unimportant.

The past history shows repeated attacks of pharyngitis and an acute attack of nephritis without known cause four years ago. Has not been robust for eight or ten years, but never confined to bed. Twenty-five years ago a prominent specialist diagnosed a tuberculous apex in the right lung. From this she seemed to have entirely recovered. Appendicitis with operation six years ago. Two years ago had amenorrhea for several months. Menses have been normal for over a year. Four months ago while travelling developed a painful swelling over an upper left molar. This was treated by a dentist seen in the emergency and he drained away a considerable amount of pus and directed her to see her dentist as soon as possible.

Present history dates from November 27, 1912, with complaint of pus about a molar four months ago, as given above but there is no trouble with the teeth at present. Patient always an active woman attending to her own affairs, but is now unable to go about without prostrating fatigue. Appetite is very poor and she sleeps but a few hours at night. For the first time in her life she finds relief in remaining in bed.

Examination. Skin very pale but mucous membrane fairly good color. Chest is negative except for soft systolic blow over heart. Abdomen negative. Over both lower extremities are pin-head purpuric spots. There has at no time been any joint pain or tenderness.

Blood Examination, December 2, 1912

Hemoglobin	90 per cent.
Red-blood corpuscles	5,600,000

Differential Count

Polymorphonuclears	61 per cent.
Transitionals	5 "
Lymphocytes	24 "
Large mononuclears	7 "
Eosinophiles	3 "
	100

Urine Examination. Reaction, acid; sugar, none; pus, none; albumin, faintest possible trace; urea, 1 per cent.; casts, none; specific gravity, 1.018.

Blood Culture. Negative for organisms (agar and broth) for twelve strains of streptococci, the fixation is positive for three.

Examination of the Teeth. Pyorrhea pocket (see Figs. 2, 3, and 4) about a twelve-year molar. At the root of a filled tooth the radiograph showed a

shadow, thought to be due to pus. Tooth was removed and filling was found to be incomplete and from this inflammation extended into the surrounding tissues. Cultures from this area were negative. The shadow in the radiograph was due to thickening of the bone and peridental membrane, secondary to the inflammation. Though the cultures from the tooth were negative the blood showed positive fixation for three out of twelve strains of Streptococcus viridans, and had this local condition remained untreated, an abscess would undoubtedly have developed as was the case with the other side of the mouth four months previous. This and Case II perhaps represent a very early stage of a local streptococcus infection with systemic manifestations. In both cases the systemic manifestations rapidly disappeared after thorough local treatment. Such cases require careful watching for the possible development of new areas of infection.

Case V.[1]—R. S., female, aged thirty years, unmarried; seen February, 1913, complaining of severe pain localized to the left tonsillar region and left ear. The pain radiates toward the mastoid and the neck posterior to the sternocleido muscle with a centre apparently in the external auditory canal. A thorough examination of the throat and ear by a specialist revealed nothing. There was no fever. The teeth were found to be exceptionally good. There was, however, tenderness on slight pressure on the gum below and posterior to the lower left third molar; the gum was slightly red and puffy. Conditions suggested an abscess, but the radiograph revealed a wisdom tooth impinging directly upon the molar and crowding that tooth. (See Fig. 1.) This condition known in dentistry as "impaction" is a frequent cause of reflex pain and without the use of the radiograph leads to much surmise with regard to possible mastoid and middle-ear disease, retrotonsillar, deep gum and dental abscesses. These cases are frequently treated by lancing the gum in the hope of liberating supposedly entrapped pus. The loss of sleep on account of the pain and disturbed digestion not infrequently lead to the impression of a systemic condition secondary to the supposed abscess. This case was surgically treated by Dr. Schamberg, who removed the offending tooth after which the patient was entirely relieved.

Summary. These cases are selected as representing five important features of general disturbance of the system, secondary to dental disease. In the first case the dental disease was detected in part and the organism determined before the joint complications developed. The use of autogenous vaccine in this case would seem

[1] This case represents a class well-known to dentists, but one with which general practitioners are usually unfamiliar. It is introduced here, however, for the information of the general practitioner in order that he may distinguish it from beginning dental sepsis with which it can be readily confused.

to have held the progress of the disease in check, but not until all of the pus areas in the teeth had been cleaned out did the systemic condition show a permanent improvement. The system, however, was probably under the influence of toxic absorption for some

FIG. 1

FIG. 2

FIG. 1.—Normal teeth, for comparison. The roots will be seen to blend with the gum, showing no areas between the teeth and gum. The gum fits snugly up to the teeth all the way up and between the roots. There is, however, in this case an impacted molar which can be seen (to the left of the picture) impinging on its neighbor. This condition may give reflex pain in the ear, neck, etc., and may be mistaken for pus formation (see Case V). It is a favorable location for the development of pus.

FIG. 2.[1]—Simple pyorrhea pockets, early stage (left lower first molar).

FIG. 3

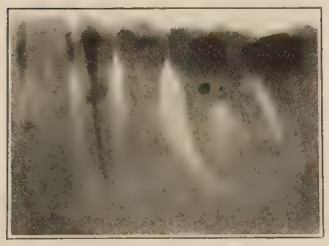

FIG. 4

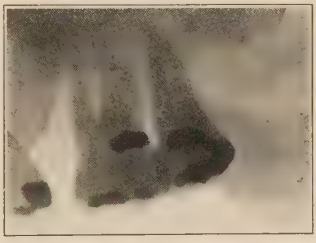

FIG. 3.[1]—Simple pyorrhea pockets; more advanced stage; no involvement elsewhere.
FIG. 4.[1]—Typical pyorrhea alveolaris; no involvement of pulp.

months before radical measures were instituted. In such cases there is always a possibility of new and independent foci of infection having been set up. Such a stage in the development of the disease

[1] If the general health is not taxed by bad food and bad air, overwork, worry, etc., the condition shown in Nos. 2, 3, and 4 may exist for long periods with or without local manifestation, but usually with moderate systemic disturbance (see Case IV). With the extension of the local process to the tooth or surrounding tissues or with deterioration in health from any cause, the system may become suddenly and seriously involved. (See Case II).

precludes the possibility of checking it by dealing with the original focus merely, and it would seem here that vaccines are our only

Fig. 5

Fig. 6

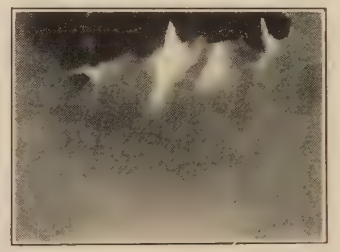

Fig. 5.—Pus in a bifurcation, discharging into the mouth. Destruction of tooth and systemic absorption imminent.

Fig. 6.—Pus pockets with necrosed roots under crowns, systemic absorption active. (See Case II.)

Fig. 7

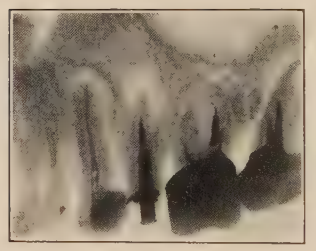

Fig. 8

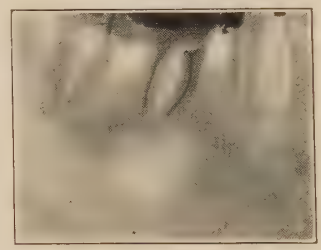

Fig. 7.—Abscesses over bicuspid roots. Advanced stage. Systemic absorption active.

Fig. 8.—Large abscess cavity: lower jaw; considerable loss of bone through septic process.

Fig. 9

Fig. 10

Fig. 9.—Chronic abscess; tooth structure entirely destroyed; tooth floating. No local symptoms, except mobility of tooth and sinking of tooth when patient chewed.

Fig. 10.—Absorption of root by abscess.

means of combating the infection. This is true of Case III, in which neither the organism was detected nor the autogenous vaccine employed until many months after the system had been

FIG. 11

FIG. 12

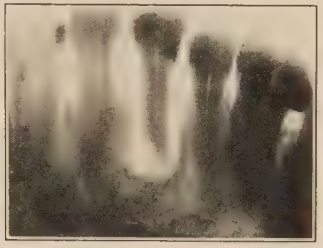

FIG. 11.—Advanced abscess; no signs or symptoms, detected by radiograph only.
FIG. 12.—Chronic abscess.

FIG. 13

FIG. 14

FIG. 13.—Combined Rigg's disease and dental abscess; chronic abscess with fistula; pulp extensively involved.
FIG. 14.—Perforated root; considerable loss of bone.

FIG. 15.—Chronic abscess; lateral root; pus draining through canal of pulp; absorption until pus was liberated.

under the influence of the infection and many joints involved, but this case also represents the ravages of septic infection of dental origin unchecked, as was common with all cases before the teeth were suspected as the original focus. Cases II and III represent possibly the earliest stage in the systemic manifestation of absorption of toxins from a dental source. Case V represents a class in which mechanical disturbance may be mistaken for an inflammatory process. From these cases and others, the following symptoms and signs may be classified. In attempting a classification it should be stated that cases of this type have not, as yet, been studied by internists and dentists together, sufficiently to make such a classification complete. It should also be stated that there are a number of characteristics which may prove of great clinical value when corroborated by thorough observation, but which for lack of such corroboration are omitted here. Such, for example, are the association of joint involvements where the upper jaw is the seat of pyogenic infection in contradistinction to an adenitis and burrowing pus when the lower jaw is involved. Again, what degree of alveolar destruction is necessary before systemic absorption takes place? Also is there any relation between tonsillar and peritonsillar and faucial infections and dental disease? In this connection Dr. Vaughan's[1] observations with regard to Vincent's bacteria and dental disease is pertinent. We are as yet without any conclusive studies on the lymphatic system draining such areas.

Symptoms. Malaise, indigestion, fetor of the breath, often intermittent; there may be periods in which the breath is so offensive as to be noticeable some little distance from the patient, while at other times such fetor cannot be detected by careful search. This is frequently called attention to by others and is rarely noticed by the patient. Loosening of the teeth, which may also be intermittent. Tenderness of the teeth on chewing; an indefinable aching of the gums; pain referred to the ear (internal and external), the mastoid, the cheek bone, the eyes, and fauces. Rapid and sometimes copious loss of hair which may occur intermittently. All the frank manifestations such as acute pain and swelling which

[1] H. S. Vaughan, D.D.S., M.D., Journal of the Allied Dental Societies, December 2, 1912.

immediately attract attention to the teeth, are omitted here, though of course they come into this classification.

Signs. A brick-red tinge about a sixteenth of an inch in width at the dentogingival margin, quite distinct from the whitish-red color of the healthy gum, marks areas of infection. These areas bleed readily on slight pressure. If a wooden spatula is run along the gum margin the diseased portions can frequently be detected by the bleeding-points left in the wake of such pressure. In more advanced cases a diseased tooth, from loosening, can be moved in its socket; a healthy tooth is absolutely immobile. Again, the gross signs such as destruction of the cemental portions, surface necroses, and visible discharge of pus, together with more obscure signs requiring instrumental examination by a dentist, are not mentioned here in detail, though they of course belong under this head. The most important point in connection with both symptoms and signs is that manifestations of systemic involvement may appear without there being any symptom referable to the teeth in which actively absorbing pus areas may be present. Such systemic manifestations, however, show marked improvement and sometimes completely disappear with the radical removal of the septic focus. Paramount among these systemic manifestations is *arthritis* and *phlebitis*. It is a noteworthy fact, however, that not until an overwhelming sepsis has developed does one procure cultures of any organism from the blood of the joint fluid. A positive complement deviation, on the other hand, from the blood is a fairly uniform finding. Fever, except in advanced cases of systemic involvement, is not common. Grave anemia of oligochromemic type may be present in the early stage of dental sepsis. Oligocythemia occurs in cases in which the system has been involved for some time. Grave secondary anemia may develop in such cases. Polynuclear leukocytosis or increase in the number of the white cells is rarely found, even when large pus areas exist in and about the teeth. Glandular enlargement seems to occur more commonly with lower- than with upper-jaw involvement. The submental and cervical glands are those most commonly affected.

Differential Diagnosis. While the occurrence of pus in and about the teeth has been found to be the cause of serious sepsis in

various parts of the system in a surprisingly large number of cases, the search for primary foci of pus, other than the teeth, must be thorough. The deep urethra, the tonsils, the peritonsillar tissues, the antrum, the posterior nares, must all be excluded. The testing out of the blood for complement-deviation for various organisms may prove the most direct evidence in the absence of local manifestation. It may be well to repeat that the blood gives negative cultures unless an advanced degree of sepsis has developed, and in such cases the condition has usually gone beyond the stage in which it can be influenced either by local, general or vaccine treatment. Case III, while the condition remained localized to one knee, was suspected of being tuberculous. Its real character was detected only when pure cultures of Streptococcus viridans from the tooth abscess, and a positive complement fixation of the blood for the same organism was obtained, the blood otherwise being negative. Fluid from the knee-joint was also negative.

Radiographs of the teeth should be placed first among the means of detecting pathological conditions in the jaw. In some instances, for example where the pus lies in a thin layer over the tooth and not in sufficient quantity to produce a pocket, nothing may appear on the plate. This occurred in Case I, when by a second examination the pus was reached by probing only.

Reference has already been made to impaction and misplacement with the consequent swelling and reflex pain which may simulate these septic conditions.

Treatment. A realization that one is dwelling with abscess cavities, due possibly to the most virulent organisms with the inevitable absorption of destructive toxins, is essential to the prompt and radical care of these cases. While it is true that the teeth (and possibly the tissues about them) resist the entry of organisms themselves into the system, the possibility of a bacteriemia always threatens such cases, with probably the development of new foci of pus in the endocardium and other vital organs. Abscesses in and about the teeth should be attacked with the same energy as pus foci in any other part of the body. Infected teeth should either be removed entire or in part by operating above the tooth through the gum, an operation now done with great skill by

many dental surgeons. Cultures should always be taken at *the time of the removal of the tooth or the operation*, and in the event of a positive culture, vaccines should be prepared and stocked in case they may be needed at some later date. Filling of the teeth and temporizing with a hope of saving a tooth which has been attacked by pus, should only be permitted after careful consultation with a competent dentist. The physician is under obligation to the patient to make him realize the seriousness of the possible consequences of the seemingly unimportant condition of the teeth. This part of the treatment cannot be too strongly emphasized, and the responsibility of temporizing with or retaining septic teeth should be placed by the physician and dentist upon the patient.

Through the courtesy of Drs. Vaughan and Tracy, already mentioned, I have the opportunity of showing radiographs illustrating the cases reported here as well as the location and distribution of pus in and about the teeth and gums.

THE COLLOIDAL GOLD REACTION IN THE DIAGNOSIS OF SYPHILITIC AND OTHER LESIONS OF THE CEREBROSPINAL NERVOUS SYSTEM

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AND
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The object of this paper is to bring to your attention a new diagnostic reaction, to record our experience with it and to further its more general application to the diagnosis of disorders of the cerebrospinal nervous system.

The senior contributor to this article became familiar with the reaction in the autumn of 1912, through having made an extended study of it under the personal supervision of its originator, Dr. Carl Lange, of Berlin.

With an enormous clinical material at his disposal Lange made a careful study of the various known clinical reactions as applied to cerebrospinal fluid in the diagnosis of syphilitic and non-syphilitic lesions of the cerebrospinal nervous system. In common with others he found that a study of the character of the cells of the cerebrospinal fluid, the quantitative estimation of albumin as determined by the ammonium sulphate and other similar reactions, and the Wassermann reaction were the most valuable diagnostic aids.

It is well known that the quantitative estimation of albumin, as determined by such methods as the precipitation of albumin by ammonium sulphate, the so-called Phase I of Nonne, is simply a group reaction. A pathological cerebrospinal fluid may contain many different albumin bodies. The Nonne reaction has to do largely with globulin and nucleoalbumin and in no way determines the relationship of the various possible albumin bodies to each

other. Lange desired to study these albumin bodies more accurately and attempted to make use of the qualitative method of albumin determinations devised by Zsigmondy.

The Zsigmondy method of qualitative albumin determination is dependent upon the peculiar property possessed by a colloidal gold solution of reacting in a characteristic way with each albumin body.

It is not the purpose of this paper to discuss at length colloidal gold reactions in general, nor to describe all the steps taken by Lange in attempting to utilize these reactions in his study of cerebrospinal fluids. The detailed accounts are accessible to all who may be interested.[1] In brief, if one brings together in a reagent glass a definite quantity of a colloidal gold solution and a given quantity of an electrolyte such as a solution of sodium chloride, the particles of colloidal gold gradually flake out and sink to the bottom of the reagent glass, leaving the solution above clear as water. This reaction is purely a physical reaction and is recognizable by the change in the color of the fluid.

Zsigmondy discovered that albumin bodies possessed the property of inhibiting or preventing the "flaking out" or precipitating action of the electrolyte.

When a definite quantity of albumin was added to a given mixture of colloidal gold and sodium chloride the colloidal gold solution retained its original color. The fine particles of metallic gold did not clump together, and thus the color of the solution remained unchanged. The protection thus afforded by the albumin is designated by the term "Goldschutz."

The inhibitive or protective action of albumin on the precipitation of colloidal gold is quantitatively different for the various albumin bodies and is constant. Under the same conditions a given quantity of an albumin body will regularly prevent a given quantity of an electrolyte from precipitating a given quantity of a colloidal gold solution.

For purposes of standardization the number of milligrams of

[1] Die Ausflockung Kolloidalen Goldes durch Zerebrospinalflussigkeit bei luetischen Affektionen des Zentral nerven-systems; Zeitschrift für Chemotherapie, 1912; Ueber die Ausflockung von Goldsol durch Liquor cerebrospinalis, Berlin. klin. Woch., 1912, No. 19.

an albumin body required to prevent 0.5 c.c. of a 10 per cent. solution of sodium chloride from precipitating 5 c.c. of a colloidal gold solution is determined and that number is applied to that particular albumin body. The term "Goldzahl" is used in this connection.

Each albumin body therefore has its characteristic "Goldzahl." It thus becomes possible by means of the colloidal gold reaction to determine whether a given albumin body is present in pure form. If it is known that the albumin body is present in pure form a quantitative estimation of it may be readily made by the colloidal gold reaction.

In attempting to apply the Zsigmondy method to the study of normal and pathological cerebrospinal fluids, Lange discovered that under certain fixed conditions to be described later, normal cerebrospinal fluids gave no reaction, while pathological cerebrospinal fluids gave a distinct reaction. He observed that under these fixed conditions all cerebrospinal fluids, giving a positive Nonne reaction, gave also a positive gold reaction, and that when the Nonne reaction was only slightly positive, the gold reaction was always more definitely positive and therefore easier to read than the Nonne reaction.

It soon became apparent to Lange that cerebrospinal fluids derived from cases in which the meninges were affected by syphilitic and metasyphilitic processes gave a very different reaction from that produced by fluids derived from cases in which the meninges were affected by non-syphilitic lesions. Thus the spinal fluid from cases of syphilitic meningitis, tabes and paralytic dementia, reacted similarly in a group by themselves and quite differently from the fluids derived from cases of suppurative meningitis, epidemic cerebrospinal meningitis, tuberculous meningitis, brain abscess, brain tumor, hemorrhage, and other non-syphilitic cerebrospinal lesions

He furthermore noted that the spinal fluid from a case of paralytic dementia reacted with the gold solution in such an intense and characteristic manner that a diagnosis of the condition might be ventured on the appearance of the reaction alone. Subsequent experience has apparently confirmed this early observation. Lange

also observed that the spinal fluid of every case of tabes gave a positive gold reaction, and in a manner definitely consistent with the gold reaction of other syphilitic lesions of the cerebrospinal meninges. It became apparent that the colloidal gold reaction was superior to the ammonium sulphate and other similar reactions in that it possessed a distinctly qualitative character. A positive Nonne reaction determines simply that the cerebrospinal fluid is pathological, but gives no clue as to the nature of the process. A positive gold reaction on the other hand likewise indicates that the cerebrospinal fluid is pathological, and in addition apparently enables one to definitely separate the syphilitic from the non-syphilitic meningeal processes.

The possibility of being able to diagnose paretic dementia upon the presence of a given type of the reaction has already been mentioned. Thus the colloidal gold reaction appears to be a qualitative reaction to a very high degree.

It would seem to surpass even the Wassermann reaction as applied to cerebrospinal fluids, in that it is qualitatively more exact, much more sensitive, and requires but a very small amount of spinal fluid. A positive Wassermann made from the spinal fluid of a case gives no clue as to the character of the syphilitic lesion. The gold reaction appears to be present extremely early in the course of syphilitic and metasyphilitic lesions of the cerebrospinal nervous system. For example, the characteristic reaction present in paralytic dementia may precede all other definite symptoms. In obscure cases of early tabes the reaction may readily be of great diagnostic value.

Its value is still further enhanced when one remembers the frequency with which the meninges are probably involved during the secondary stage of syphilis without symptoms. Our experience confirms that of Lange who found that it required a much larger quantity of cerebrospinal fluid than is ordinarily used to obtain a positive Wassermann reaction. Fluids that react negatively to the usual quantity advised may give a positive reaction when a sufficient quantity is used.

The intensity of the gold reaction is a fair index to the amount of spinal fluid that should be used in order to obtain a positive

Wassermann reaction. If the gold reaction is intense, such as occurs in the most pronounced reactions of paretic dementia, a positive Wassermann may be obtained by using the same dilution of cerebrospinal fluid as of blood serum. A well-developed case of cerebrospinal syphilis may give a negative Wassermann reaction unless a quantity of spinal fluid five or ten times greater than that employed in the blood-serum test is used.

In testing spinal fluids in cases that have been treated, and particularly cases that show a weak gold reaction, forty or fifty times the quantity that is used for the serum test may be required to give a positive Wassermann reaction. In many cases it is impossible or inadvisable to withdraw such a large quantity of fluid for diagnostic purposes. Thus 0.2 c.c. is sufficient for the gold reaction; 12 to 15 c.c. may be required to obtain a positive Wassermann reaction.

The great difficulty surrounding the application of the test is in the preparation of a suitable gold solution. Unless this important reagent is absolutely correctly prepared the test will invariably prove valueless.

A solution of metallic gold in colloidal condition may be produced according to the method of Bredig,[1] by the passage of an electric current in the form of an arc, between two gold points under pure water. Lange employed the older method adopted by Zsigmondy which consists in the reduction of gold chloride with formaldehyde in a dilute slightly alkaline solution.

If one wishes to avoid disappointment in the preparation of the colloidal gold solution according to this method the following detailed procedure should be unqualifiedly, accurately followed.

The following stock solutions may be kept for use in making the colloidal gold solution. The chemicals must be pure and solutions accurately made.

1. One per cent. solution of gold chloride (aurum crystallizatum flavum Merck).

2. Two per cent. solution pure potassium carbonate (Merck reagent).

3. One per cent. solution of ordinary formalin.

[1] Zeitschrift f. Elektrochem., 1898, Band iv, pp. 514, 547.

The above solutions should be made with double distilled water and the gold chloride solution kept in a dark bottle stoppered with cork. To avoid contaminating the gold chloride stock solution by the introduction of a pipette, a small quantity should be poured into a glass beaker preparatory to making the colloidal solution.

To prepare the solution, 500 c.c. of freshly double distilled water are placed in an open Jena glass vessel of the capacity of about 1500 c.c. For this purpose commercial distilled water cannot be used. Commercial distilled water freshly redistilled may yield good results, but the first 200 c.c. distilled should be thrown away, otherwise the resulting gold solution is likely to be bluish red in color.

By means of an intense flame, without asbestos protection, the water heated slowly at first is finally brought quickly to the boiling point. During the latter part of the heating process 5 c.c. of the 1 per cent. solution of gold chloride is added and immediately thereafter 5 c.c. of the 2 per cent. potassium carbonate solution, the mixture now about ready to boil is still further heated until it just begins to boil. The flame is then turned off and 5 c.c. of the 1 per cent. formalin solution is quickly added, but only a portion at one time, and while the fluid is vigorously agitated to insure a rapid and even distribution of the formalin solution. At first the solution assumes a pale rose color, then the color becomes gradually darker until finally a beautiful purplish-red shade of color appears. The color of the solution is of extreme importance. Solutions bluish in color or that are distinctly smoky in appearance do not give reliable results. When properly prepared the solution appears, perfectly clear both by reflected and transmitted light, the color is a deep red with a slightly purplish tinge and the best solutions show a faint suggestion of a yellowish tone. The lighter the color the less intense the reaction. If the solution is dark red or bluish in color the reaction is too intense and the results of the test are unreliable.

The production of dark, smoky, or otherwise unsatisfactory fluids usually results from the use of improperly distilled water, or imperfectly cleaned utensils, or too much potash solution. The greater the quantity of potash used the darker the solution. The

potash solution must therefore be made accurately. If by chance that particular potash solution does not yield a good, clear solution of proper color, a slightly larger or smaller quantity of the potash solution may be used each time until the resulting fluid is satisfactory. While testing out the chemicals 200 c.c. of distilled water, 2 c.c. of the 1 per cent. gold chloride solution and 2 c.c. of the 1 per cent. formalin solution may be used. When the right combination is found the same relative amounts of these particular stock solutions should be used in making up larger quantities of the gold solution. It is impractical to attempt to make up more than 500 or 1000 c.c. at one time. The manner in which the fluid is heated is of very great importance. It should be finally rapidly brought to a boil with an intense flame. If the fluid is seen to vaporize noticeably before it boils the red color may not appear after the addition of formalin. Experience in making the solution will soon demonstrate that it is unwise to ignore seemingly unimportant details. Unreasonable as it may appear the shape and quality of the glass in which the mixture is brought to a boil has an influence on the character of the solution. Lange accidently discovered that he could make a better gold solution in an open glass beaker than in an Erlenmeyer flask. He subsequently learned that this fact had already been established by the experience of others. Lange urges the use of a beaker made of Jena glass. He relates that the substitution of a rubber cork connection in his distilling apparatus rendered it impossible for him to produce a satisfactory gold solution until he discovered the reason for the failures and replaced the ordinary cork connection. There is less risk in using a distilling apparatus with ground-glass corks, although well cleansed, ordinary cork will yield satisfactory results.

It is to be understood that all glassware used in connection with the test is to be most carefully cleaned. It is difficult to wash all alkali out of glass utensils, therefore it is best to clean by first using a mixture of 25 per cent. raw sulphuric acid and 10 per cent. potassium bichromate solution, then wash thoroughly with tap water and then with distilled water. When all directions for making the gold solution are accurately followed the resulting fluid is likely to be satisfactory upon first trial. Once properly prepared

the solution will not deteriorate for many months. It may be kept conveniently in a large Erlenmeyer flask stoppered with gauze. The introduction of a clean 50 c.c. pipette at each test will not contaminate the solution.

The Nonne reaction should be regularly used as a control. The saturated ammonium sulphate solution may be made and kept in a small Erlenmeyer flask stoppered with gauze or cotton. If made by the cold process the solution requires no care other than to add a sufficient quantity of ammonium sulphate to the distilled water and allow it to stand for two or three days shaking the solution now and then to insure complete saturation. If compelled to make a solution on short notice one may use ammonium sulph. 80; distilled water, 100. Heat gently, otherwise the solution will become acid in reaction. The solution must be neutral to litmus.

The application of the test is relatively simple, requiring only careful laboratory technique. The cerebrospinal fluid should be withdrawn into an absolutely clean reagent glass or test-tube. The needle used for lumbar puncture should be carefully prepared. Each time after use, it is well to thoroughly cleanse the needle with salt solution, alcohol and ether, then place it in a test-tube stoppered with cotton and sterilize with dry heat. Thus prepared the needle will not rust, and will always be ready for use. If puncture is carefully made bleeding can be avoided in most cases. Better results are obtained if puncture is made directly in the median line. If considerable blood appears the fluid will be valueless for chemical tests such as the Wassermann, Nonne, and gold reactions. In some cases only the first portion of the fluid that escapes contains a sufficient quantity of blood to render the tests valueless. A second portion caught separately may give modified reactions of diagnostic value. Fluids containing enough blood to show a sediment of red cells after centrifuging should not be used. The Wassermann reaction will permit a greater quantity of blood than the Nonne or gold reactions.

In general when but a few red cells are present, the Nonne reaction may be judged positive if at the end of three minutes a very pronounced precipitate is present. A faint precipitate at the end of twenty-four hours or visible opalescence after three

minutes should be considered valueless when the microscope reveals red cells in the spinal fluid. Normal spinal fluid, entirely free from blood, will rarely if ever show a real precipitate after twenty-four hours. The best time for reading the Nonne reaction is at the end of three minutes.

The gold reaction will permit of the presence of as much blood as the Nonne; and the modified reaction retains the same qualitative advantages. The manner in which the gold reaction is modified by a small quantity of blood will be described later.

The test is applied in the following manner: Eleven test-tubes of uniform size, approximately three-quarters of an inch in diameter, previously carefully cleaned, with the acid and bichromate mixture, followed by alcohol and ether, and then sterilized with dry heat (latter not necessary) are placed in a test-tube rack. Ten of the tubes are to be used for the gold test, the eleventh tube is reserved for the Nonne reaction. A 0.4 per cent. solution of sodium chloride is made by adding 4 c.c. of a 10 per cent. stock solution of sodium chloride to 100 c.c. of distilled water. The 0.4 per cent. salt solution must be made fresh. Using at 12 c.c. pipette, 1.8 c.c. of the 0.4 per cent. salt solution is placed in the first test-tube and 1 c.c. in the other nine tubes. Using a graduated 1 c.c. pipette, next draw up 0.7 c.c. of the spinal fluid to be examined, and put 0.2 c.c. in the first tube and 0.5 c.c. in the eleventh tube; add 0.5 c.c. of concentrated ammonium sulphate solution to the eleventh tube, thus preparing the Nonne reaction which is to be read at the end of three minutes. Meanwhile complete the gold test using a fresh 1 c.c. pipette. Mix thoroughly the contents of the first tube which now contains 2 c.c. of a 1 to 10 dilution of spinal fluid (1.8 c.c., 0.4 per cent. salt solution and 0.2 c.c. spinal fluid). Draw up 1 c.c. of this mixture and add it to the second tube, mix thoroughly. The second tube now contains 2 c.c. of dilution 1 to 20. Draw up 1 c.c. of this mixture and add to the third test-tube, and so on making dilutions $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{80}$, $\frac{1}{160}$, $\frac{1}{320}$, $\frac{1}{640}$, $\frac{1}{1280}$, $\frac{1}{2560}$, and $\frac{1}{5120}$. The tenth tube contains 2 c.c. of the last dilution. One c.c. of this is thrown away so that each of the ten tubes now contain 1 c.c. of dilutions, ranging from $\frac{1}{10}$ to $\frac{1}{5120}$. The final step is to add 5 c.c. of the gold solution to each of the ten test-tubes. A 50 c.c.

pipette is most convenient for this purpose. To prevent partial reactions, the gold solution should be added to each tube in such a way as to insure rapid and thorough mixture of its contents. A record is now made of the Nonne reaction that has taken place in the eleventh tube. All having had experience with Nonne reaction know that the finer positive reactions are likely to be overlooked until one has acquired skill through experience in reading the reaction.

If Nonne is strongly positive, the gold reaction usually begins to show a distinct change within a very short time after the test has been completed. The reaction is ready for its final reading in all cases on the following day or within eighteen to twenty-four hours. The finer reactions are not visible in artificial light.

If all solutions and dilutions are properly made, normal spinal fluid free from blood will produce no change in the appearance of the gold solution. All tubes will look alike. If the gold solution is slightly darker than the best solutions, normal spinal fluid may give a faint reaction perceptible at dilutions about 1 to 40 to 1 to 80. Such faint reactions are best made visible by placing the tube containing the weakest dilution alongside the tubes in which an apparent change has occurred. Gold reactions when pathological are so very pronounced that they are distinctly visible and without the aid of refined comparisons.

The gold reaction is more delicate than the Nonne reaction, hence the experience of Lange is likely to be duplicated by all who use it. Lange states that in his early work he now and then recorded the Nonne reaction negative at the end of three minutes. The next day the gold reaction showed such a postive change that he is now sure that he had at that time not acquired sufficient skill in reading the finer positive Nonne reactions.

In describing the physical properties of the reaction, it may be said in general that spinal fluids derived from syphilitic and meta-syphilitic processes involving the meninges give a reaction toward the lower dilutions; fluids from non-syphilitic processes react in the higher dilutions.

For example, syphilitic fluids react with maximum intensity at dilutions $\frac{1}{40}$ and $\frac{1}{80}$. Non-syphilitic fluids react in a position

removed to the right and with maximum intensity in the region of dilution $\frac{1}{640}$ or in still higher dilutions.

The colored plates in this article are reproductions of reactions that actually occurred in our series. These reactions are fairly typical. It will be noted that there is a tendency for the reaction to take place in the form of a curve. Such curves are represented by charts made according to the usual method. The numbers placed upon the abscissa represent the dilutions of the spinal fluid with 0.4 per cent. salt solution. The names of the various colors ranging from red to white or colorless are arranged along the ordinate.

Chart I represents the curves in cases of cerebrospinal syphilis. The smooth line corresponds to the curve most commonly found in our series.

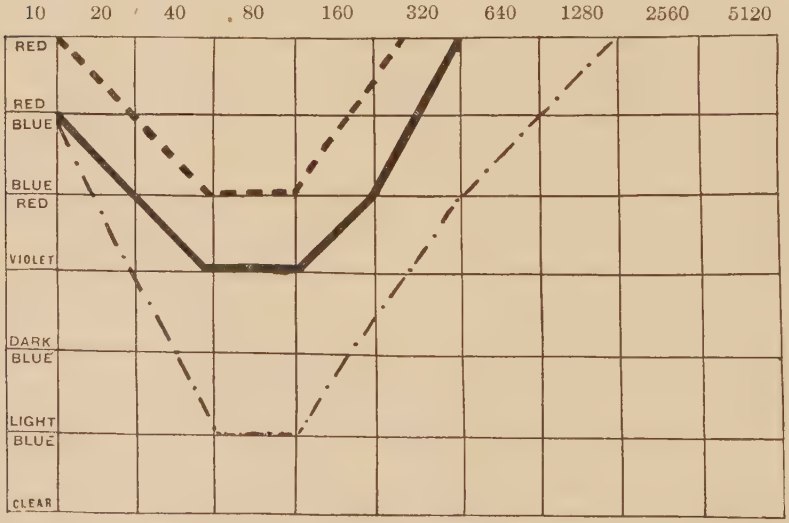


CHART I.—Cerebrospinal syphilis (acquired and congenital). Typical reaction is reproduced in colored plate No. I.

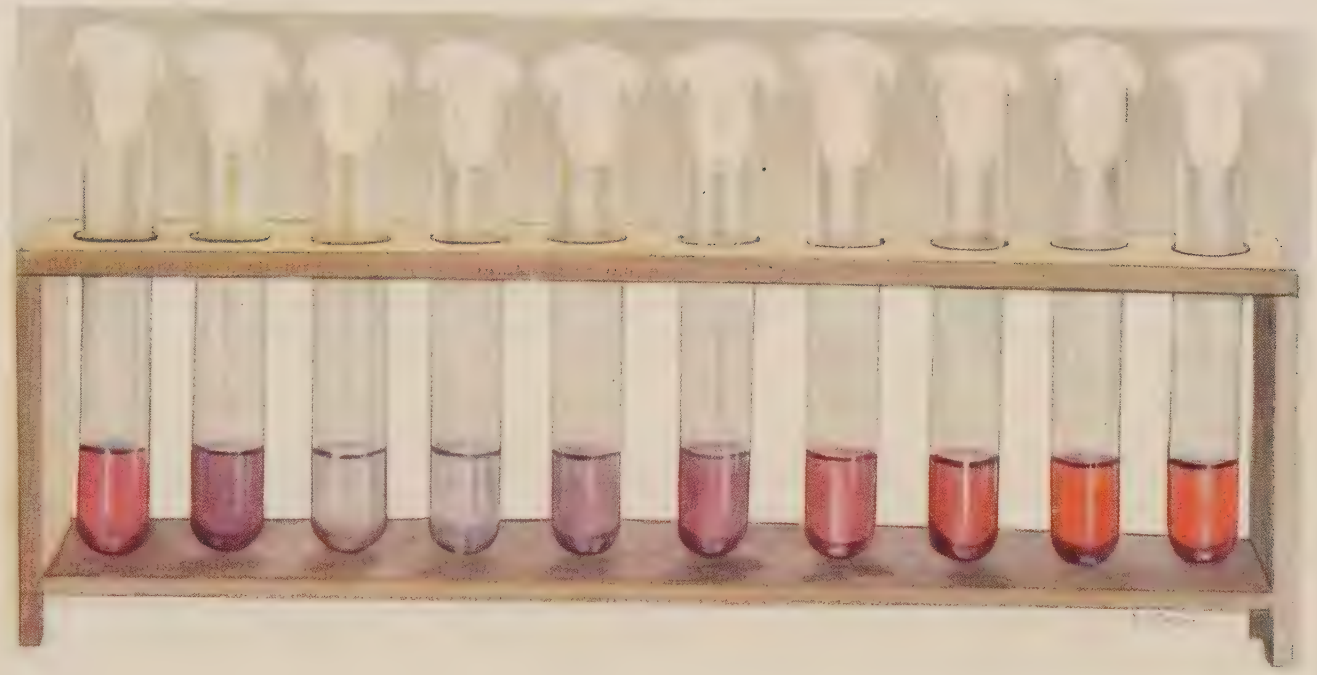
The reactions vary in intensity. The dotted lines represent the limit of variations in our cases.

It will be seen that the maximum change is at dilutions $\frac{1}{40}$ and $\frac{1}{80}$.

Chart II represents the curves produced by our cases of tabes. Again, the smooth line corresponds to the curve most commonly

PLATE I

Cerebrospinal Syphilis



Tubes

present. The dotted lines represent the extremes of variation noted in our series.

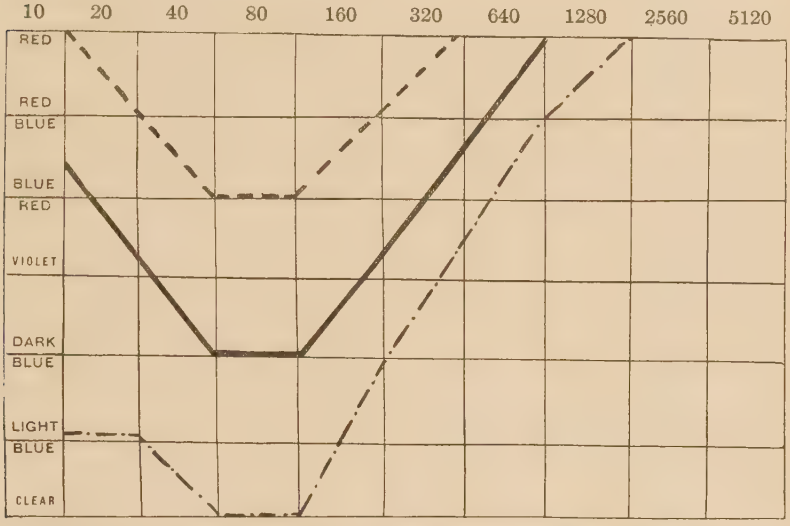


CHART II.—Tabes. Typical reaction is reproduced in colored plate No. II.

Chart III represents the curves in paretic dementia. The intensity of the reaction is greatest in this disease. It will be noted that the curves represent the fluid as colorless toward the left or in the stronger dilutions. As a rule the precipitation is nearly or quite complete at dilutions $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{80}$. It is very common for the fluid to be practically colorless in dilutions $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{80}$, $\frac{1}{160}$ and $\frac{1}{320}$. In the higher dilutions the reaction gradually shades off showing, however, a decided change in dilutions as high as $\frac{1}{5120}$. In only one of our series did the fluid fail to be colorless at dilution $\frac{1}{10}$.

Lange has observed complete precipitation in all dilutions up to $\frac{1}{5120}$ with a blue red color in dilution $\frac{1}{20000}$. Even when the reaction is so very intense that all tubes from $\frac{1}{10}$ to $\frac{1}{640}$ dilution look practically alike and colorless, it may usually be shown that the reaction is strongest at dilutions $\frac{1}{40}$ and $\frac{1}{80}$. This may be demonstrated by making the dilutions of the cerebrospinal fluid with weaker salt solutions. Not all cases of paretic dementia

cause complete precipitation. Lange reports a curve such as is represented by the upper line in our Chart III.

If a tabetic shows a reaction approaching the intensity of a paretic dementia, clinical experience would seem to indicate that one may be justified in suspecting the presence or development of tabo-paresis. In all syphilitic and metasyphilitic meningeal processes the intensity of the Nonne reaction runs fairly parallel with the intensity of the gold reaction. This is not true of the non-syphilitic processes.

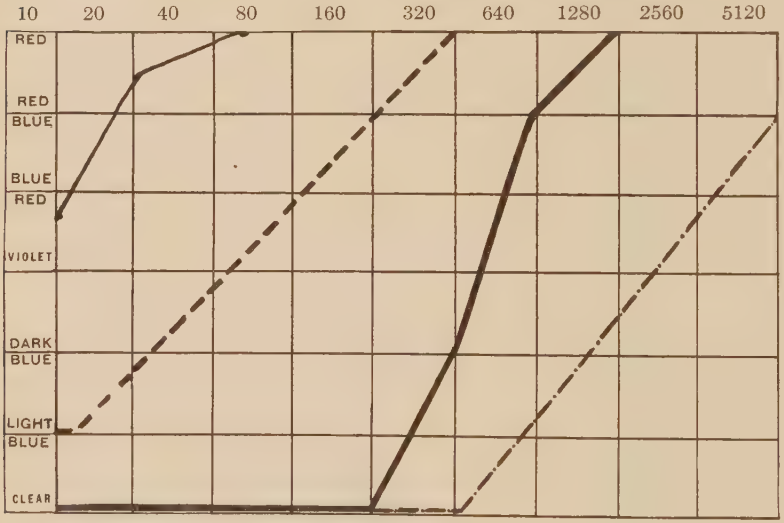


CHART III.—Paretic dementia. Typical reaction is reproduced in colored plate No. III.

Chart IV represents the curves usually produced by fluids derived from cases of suppurative meningitis, including the epidemic cerebrospinal types. It will be observed that the curves are in a decidedly different position from those representing the syphilitic processes. The average maximum intensity of these reactions occurred at approximately dilutions $\frac{1}{320}$ and $\frac{1}{640}$ and the whole curve is far to the right of the curve produced by syphilitic disease.

Chart V represents the curves present in our cases of tuberculous meningitis.

Paretic Dementia

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PLATE IV

Tuberculous Me[illegible]

Lange observed that the spinal fluid from tuberculous meningitis seemed to show a tendency to react in dilutions stronger than

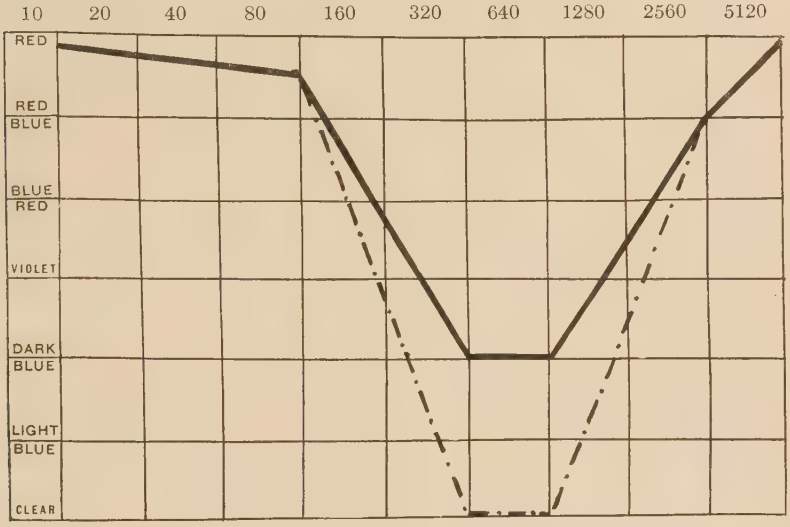

CHART IV.—Suppurative meningitis.

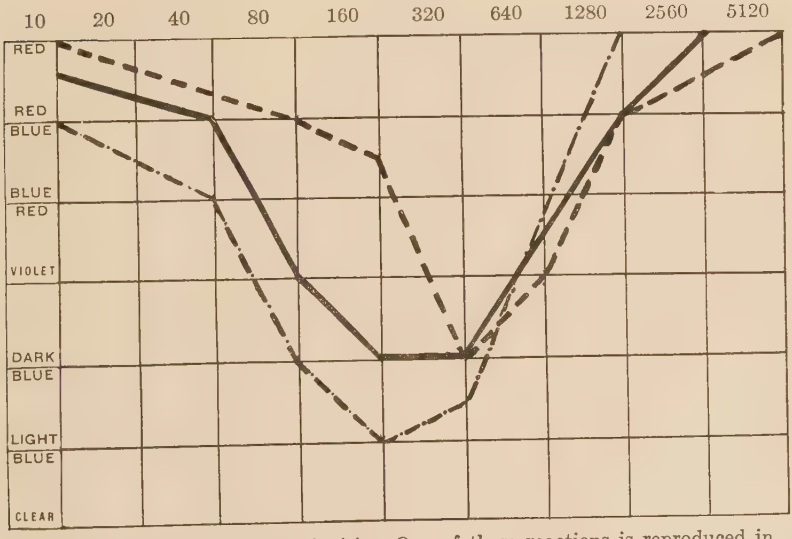

CHART V.—Tuberculous meningitis. One of these reactions is reproduced in colored plate No. IV.

fluids derived from the suppurative types. Our series would seem to corroborate that observation. The maximum intensity of the reaction was near dilution $\frac{1}{160}$. Possibly the future may demonstrate that tuberculous meningitis reacts regularly more to the left than the other types of non-syphilitic disease of the meninges.

In our series included 36 cases of congenital syphilis. So far as we know the gold reaction had not been applied to the cerebrospinal fluid of congenital syphilis prior to these tests. It was found that a positive Nonne and positive gold reaction is practically the same as that found in acquired cerebrospinal syphilis.

If the future demonstrates that the gold reaction is positive in all or many cases of congenital syphilis the value of the reaction will be enormously increased.

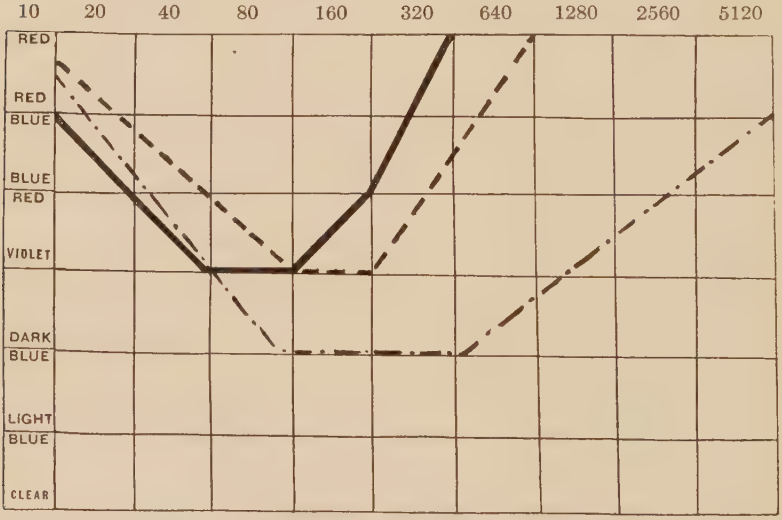

CHART VI.—Cerebrospinal syphilis. Showing influence of contamination with microscopic and macroscopic quantities of blood.

We are particularly indebted to Dr. Grulee for having furnished the spinal fluids of nearly all of the cases of congenital syphilis tabulated in this article. Our work on these fluids was the basis of the article by Grulee and Moody published in the *Journal of the American Medical Association*, July 5, 1913. Nearly all of

the children from whom the spinal fluids were removed were less than six months old.

Chart VI shows the effect of blood on the reaction. The smooth line represents the curve of a cerebrospinal syphilis. The dotted line shows how the reaction is modified by the presence of a microscopic quantity of blood in the spinal fluid of the same case. The dashed line shows the effect of a macroscopic quantity of blood contamination.

The conditions under which the gold test may be applied when the spinal fluid is contaminated with blood have already been discussed.

Disease	No. of cases	Strongest at 40–80	Strongest to right of 40–80	Nonne	Wassermann-Noguchi Positive	Wassermann-Noguchi Negative	Average cells per c.mm.
Paretic dementia	33	33	0	++	33	0	75
Tabes	49	49	0	+	31	17	34
Cerebrospinal syphilis	43	43	0	+	21	19	15
Congenital syphilis	36	36	0	±	12	19	7
Tuberculous meningitis	14	0	14	++	0	14	125
Suppurative meningitis	15	0	15	+++	0	15	not counted
Miscellaneous (no reaction)[1]	40	0	0	0	0	40	3
Miscellaneous (slight reaction)[2]	38	3[3]	35	±	2[4]	36	3

[1] These cases "miscellaneous (no reaction)" include spinal fluids from cases of trifacial neuralgia, neurasthenia, diabetes insipidus, polyneuritis, brain tumor, amebic dysentery (with positive Wassermann blood reaction), edema of brain (toxic), epilepsy, pernicious anemia, otitis media with meningismus, anterior poliomyelitis (one case one day after onset, etc.).

[2] These cases, "miscellaneous (slight reaction)," include spinal fluids from cases of brain abscess (4 cases), status lymphaticus, acute encephalitis (2 cases), brain tumor, tumor of cord, spinal caries, anterior poliomyelitis (five and one-half months after onset), sinus thrombosis, syringomyelia, pneumonia with meningismus (4 cases), uremic coma.

[3] Two of these (3 strongest at 40 to 80) were cases of cerebellar abscess confirmed by operation and autopsy, staphylococcus infection, no gross evidence of meningitis, both in boys ten years old. Third case was one suspected of congenital syphilis in a child, aged seven months; reaction resembled paretic dementia. The infant died two days after puncture was made; no autopsy.

[4] One of these cases was that of a tumor of the spinal cord (non-syphilitic). The other was one of the cases of cerebellar abscess described in the text.

The Noguchi modification of the Wassermann was used in the entire series (1 c.c. of suspension of human corpuscles—corpuscles from the same individual used throughout); fresh guinea-pig serum (2 units); antihuman rabbit serum (2 units); alcoholic extract of fetal luetic liver as antigen in about one-half of the series, and acetone insoluble fraction of extract of beef heart in the remainder.

The relatively large number of negative Wassermann reactions obtained in our cases of tabes, cerebrospinal syphilis and congenital syphilis, is due, we believe, to the use of too little spinal fluid. In the early part of the work only 0.25 c.c. was used.

We have thus far applied the test to the spinal fluids of 268 different cases as tabulated. This series does not include the reactions observed in Berlin by the senior contributor.

The Nonne reaction was invariably used as a control. With the exception of the cases of suppurative meningitis a cell count was made in practically every case. As may be noted by the figures, a Wassermann-Noguchi test was made in nearly every case. It was omitted only because of the lack of sufficient fluid. The Noguchi butyric acid reaction was used on many of the fluids first tested and was found to parallel the Nonne reaction.

Conclusions. As a result of our observation and study of the Lange colloidal gold reaction we are convinced of its very great and unusual value. As is well known, no sign, symptom, or test in medicine is absolutely pathognomonic.

Of the 268 different fluids tested the reactions were apparently misleading in only two or three instances. As is stated in the note descriptive of the tabulated cases, fluids were obtained from two children ten years of age, both afflicted with cerebellar abscess, due to staphylococcic infection. The fluids in both cases reacted strongest at dilutions of 40 to 80. The spinal fluid of one of these cases gave a positive Wassermann. The fluid from the other case gave a negative Wassermann reaction. Autopsy revealed cerebellar abscess and it was reported to us that there was no evidence of syphilis.

The third case in which the reaction may have been misleading was a case of suspected congenital syphilis. The fluid in this case gave a reaction resembling that of paretic dementia. The infant died two days after puncture, and autopsy was not obtained.

In all other cases tabulated, error would seem to be as completely eliminated as is possible. Every fluid giving a positive Nonne reaction gave also a positive gold reaction. The gold reaction never appeared as a distinct reaction when all other tests indicated that the fluid was normal.

In all of our cases of syphilis with meningeal involvement, the intensity of the colloidal gold reaction was very parallel to the intensity of the Nonne reaction. In the non-syphilitic types of disease such parallelism does not occur. For example, suppurative

meningitis may give a very intense Nonne reaction and only a very moderate gold reaction.

The characteristic reaction for syphilis (strongest at dilutions 40 to 80) was present in every case of paretic dementia, tabes, cerebrospinal syphilis, and congenital syphilis. It was not absent in any type of syphilis in which the meninges were involved.

The various forms of suppurative meningitis invariably gave a reaction with greatest intensity to the right of the characteristic reaction for syphilitic fluids. As is shown in the charts these fluids reacted with greatest intensity at dilutions about 640 to 1280.

Our cases of tuberculous meningitis, toxic edemas, encephalitis, and brain tumor reacted, as a rule, about midway between the fluids of syphilis and the suppurative types of meningitis. The strongest reaction was at dilutions 160 to 320. In tuberculous meningitis the Nonne reaction is strong and the cell count is relatively high (see tabulated cases). In the other diseases reaction with maximum intensity in dilutions at which the fluid of tuberculous meningitis reacts strongest, the cell count is low and the Nonne reaction is faint. It would therefore appear that by combining the Lange reaction with the cell count and the Nonne reaction, the diagnosis of tuberculous meningitis may be greatly facilitated.

Finally, it is to be understood that the colloidal gold reaction does not supplant the Wassermann reaction and is of use only in determining the presence or absence of pathological changes in the meningeal fluid. The reaction should not be expected in cases of syphilitic infection in which there is no meningeal involvement. In such cases a Wassermann applied to the blood serum might readily be positive. The frequency with which the meninges are involved in syphilis without definite meningeal symptoms has already been mentioned. The superiority of the colloidal gold test to the Wassermann reaction as applied to the spinal fluid has been discussed.

DISCUSSION

Dr. R. C. Cabot: Has the reaction been tried with blood serum?

Dr. Sippy: Yes; but it is not so delicate as with the spinal fluid.

Dr. C. F. Hoover: What relation does the reaction bear to the cellular content of the subarachnoid fluid?

Dr. Sippy: The agreement between the findings of the colloidal gold reaction and the evidence obtained from examining the cellular content of the spinal fluid is fairly constant.

ON SOME ANGIONEURAL ARTHROSES (PERIARTHROSES, PARARTHROSES) COMMONLY MISTAKEN FOR GOUT OR RHEUMATISM

By SOLOMON SOLIS COHEN, M.D.
PHILADELPHIA

Among the diverse and often puzzling phenomena that, under appropriate exciting and determining influences, occur and recur in the subjects of angioneural imbalance (*vasomotor* or *autonomic ataxia**) are pains and swellings in and around the joints. These are sometimes accompanied with fever; and, whether febrile or afebrile, the morbid complexus is commonly mistaken for gout or rheumatism.

Diagnosis and, in consequence, prognosis and treatment depend upon recognition of the underlying constitutional condition or diathesis. In other words, there must be a diagnosis of the patient, as well as of the particular collocation of symptoms that he (or she) happens to present at the moment. I have, before this Association[1] and elsewhere,[2] fully and repeatedly described the physical

* ". . . Ataxia rather than hyperkinesis, or hypokinesis, because excessive vascular dilatation and excessive vascular constriction may be either spastic or paretic, or both spastic and paretic, as dilator or constrictor nerves, or both, are affected; and even in the extreme and opposite types of vasomotor ataxia, the phenomena, while always more or less paroxysmal, are neither exclusively those of dilatation nor exclusively those of constriction, but both abnormal dilatation and abnormal constriction are usually present in varying degrees in the same patient. The influences under which these phenomena are displayed are, more especially, temperature—and cold more than heat—emotion, visceral, or external reflex excitation, and the action of toxic agents formed in the organism or introduced from without." From the author's paper of 1894. *Cf.* recent discussions anent "sympathicotonia" and "vagotonia." Following Langley's use of words, according to scientific precedent, I prefer to consider the autonomic or sympathetic system as a whole. Its fibers and ganglia may properly be classified according to function upon pharmacological or other data—but to upset recognized terminology merely causes confusion.

and functional characteristics and simple test reactions by which this diagnosis is to be made; and more recently Morichau-Beauchant[3] in France, Herz,[4] Eppinger and Hess,[5] and Karl von Noorden[6] in Germany, Barker and Sladen[7] in this country, and others have in various connections repeated and somewhat amplified the descriptions. Among the writers cited, Herz, and Barker and Sladen make due acknowledgment of the earlier observations.*

* It may prove interesting, or at least amusing, to compare certain of the statements concerning vasomotor ataxia and its relations to idiosyncrasies, contained in the communication read by me before the First Pan-American Medical Congress (1893) and published in its Transactions (also in the American Journal of the Medical Sciences, February, 1894) with certain paragraphs in the paper published by Morichau-Beauchant in *Le Progrès Médical*, April 16, 1910, and in Herz's monograph of 1902. The sources of the citations are sufficiently indicated by their language—English, French, and German respectively. I have permitted myself to emphasize by small capitals in two of the French citations, and by italics in the German citation, an essential difference between the writers.

"For every idiosyncrasy there must be a physiological basis. By comparing the phenomena, special and general, exhibited by a group of persons presenting similar or identical idiosyncrasies, we take a step toward the recognition of the basic physiological conditions."

"*Force nous est donc de faire intervenir une prédisposition spéciale, un terrain commun, qui permettra aux diverses manifestations qui ont fait l'objet de notre étude de se produire. Or, à cet état morbide constitutionnel, nous avons donné le nom . . . de* DIATHÈSE ANGIONEUROTIQUE."

"I would invite attention to an idiosyncrasy of the circulatory mechanism, which, in its extreme degrees, manifests itself in the form of well-recognized symptom-complexes; in its minor degrees gives rise to puzzling manifestations of great variety of detail; and in its least developed forms often passes unnoticed. For this condition —which seems to depend upon a feebleness in the coördinating mechanisms, in consequence of which the balance of the cardiovascular action becomes disturbed by influences that in the great majority of persons have no such effect, and greatly disturbed by influences that normally have slight effect, while the restoration of equilibrium is slow and imperfect—I would propose the self-explanatory name of *vasomotor ataxia*. . . ."

". . . By the term *vasomotor ataxia* it is proposed to designate the condition of instability of the mechanism of circulation present in certain persons and characterized by abnormal readiness of disturbance, with tardiness of restoration, of the equilibrium of the cardiovascular apparatus. The manifestations are most strikingly displayed by the heart and by the cutaneous peripheral vessels, but analogy indicates the occurrence of similar phenomena in the vessels of the glands and of the viscera, more especially in those of the kidney, of the gastro-intestinal tract, and of the brain."

"Vasomotor ataxia may be acquired as a sequela of disease; in many cases it is congenital; in some cases inherited; the condition is not rarely present in several members of a family."

"Among other symptoms and morbid associations observed are anemia, hysteria, drug and food idiosyncrasies, urticaria, local (circumscribed) edema, hyperidrosis, angina pectoris and pseudo-angina, organic heart disease, pulmonary tuberculosis, asthma, hay fever, vertigo, migraine, and other forms of headache, transient hemiopia and other visual disturbances, persistent mydriasis, . . . menstrual irregularities, intermittent polyuria, rheumatism, rheumatoid arthritis, contractures

The present communication may therefore be confined to a discussion of the special syndrome group to which it is desired once more to direct the attention of physicians.

In the title of the paper, the clinical pictures to be described have been designated *angioneural arthroses*. This term, however, is not entirely satisfactory. It implies, correctly, that the nosologic species embraces several varieties. It indicates, moreover, that we are not dealing with true inflammation—*arthritis*. But it is not sufficiently comprehensive. In some, and perhaps the majority of cases, the edema of overlying tissues is more important than the effusion (or other change) within the joint; in still other cases, the joint structures proper are not manifestly involved. For these the term *periarthroses*—or even *pararthroses* when it is only the neighboring soft parts that are affected—would be more suitable.

The term "*hydrops articulorum periodica*" or "*hydrops articulorum intermittens*" has been applied to the one variety of vasomotor joint disorder that has thus far been definitely recognized;* but it is applicable to that variety only. The number of varieties seems,

of digits, chorea, epilepsy, neurasthenia, neurotic dyspepsia, gastralgia, enteralgia, membranous enteritis . . . as effects of a common cause, or as secondary results."

"*La diathèse angioneurotique*, DISIONS-NOUS, *est une prédisposition morbide héréditaire et familiale caractérisée par une instabilité particuliére de l'appareil vaso-moteur, qui rend celui-ci, chez les sujets qui en sont atteints, apte à répondre par des réactions excessives à des irritations qui chez d'autres resteraient sans effects. Son domaine est des plus étendus. Il comprend: des troubles du côte de la peau: urticaire, œdémes aigüs circonscrits, érythèmes divers, auxquels s'ajoutent des manifestations nombreuses du côté des muqueuses et des viscères; crises gastro-intestinales, idiosyncrasies alimentaires et médicamenteuses, hypersensibilité de la pituitaire aux odeurs, asthme des foins et asthme vrai, migraines, etc.*

"Nur Solis-Cohen hat die Wichtigkeit, die Haufigkeit und die klinische Stellung der im weiteren zu schildernden Krankheitsbilder erkannt. *Er nannte* den sehr mannigfaltigen Zustand, 'welcher auf einer Schwäche in dem Coordinations-mechanismus beruht, infolge wovon das Gleichgewicht der Gefassaction von Einflüssen gestört wird, die bei der grossen Mehrheit aller Menschen keine solche Wirkung haben, und sehr gestört von Einflüssen, die normaler Weise nur eine kleine Wirkung haben, während die Herstellung des Gleichgewichtes langsam und unvollständig ist'—er nannte diesen Zustand '*vasomotor ataxia*.' Ich glaube, dass dieser Name als kurze Bezeichnung beizubehalten ist."

"In many striking cases there has appeared to be morbid alteration in the thyroid gland."

Il existe des presomptions en faveur de l'origine thyroïdenne des divers troubles relevant de la diathèse angio-neurotique.

* This was apparently first observed by Perrin (1845); then by Moore (1852, 1865). Fridenberg (1888) was the first American reporter. Schlesinger (1900) has made the most comprehensive study of the subject.

however—as in all the related syndromes constituting the several species of the nosologic genus *ataxia autonomica**—to be limited only by the possibilities of variation; while the limits of variability approach closely the full extent of the possible permutations represented by the number of symptomatic and other factors.

To adopt the ancient Cnidian precedent and describe each variation of a variety as a separate species would, indeed, accord with the method of many writers upon neurovascular disorders; but my own endeavor for the last twenty-five years has been to group rather than to separate; to bring out the underlying unity rather than to accentuate the superficial diversity. Besides which, as I have repeatedly pointed out in regard to the whole subject, as well as to other special phases of it, such a course would ordinarily result in the ascription of a new diagnostic name to each recurrence of the disorder in nearly every individual. It is true that in a very few persons the successive attacks are relatively consistent—or rather, monotonous—in type; but this only emphasizes the general capriciousness and whimsicality of the phenomena.

The chief *symptomatic elements* are pain, swelling, discoloration, and fever.

Pain and *swelling* are usually associated, and frequently develop, subside, and reappear together. Either, however, may be present without the other. Sometimes they alternate; sometimes they appear and disappear without any evident mutual relation. The extent of the swelling, moreover, is never an index to the degree of pain, whether directly or inversely; there may be intense pain with no swelling or considerable swelling with no pain. Either symptom may precede, either may outlast, the other.

The swelling may be *due* to effusion into the joint or to edema of the overlying soft parts, or both. Sometimes the painful joint and the tissues about it are not swollen, but a lump or lumps will appear on the limb, at a greater or less distance above the joint (*cardiad*).

The pain is ordinarily *referred* to the joint or joints apparently

* Strictly speaking, autonomic ataxia is not a nosologic genus in itself, but the substratum upon which a nosologic genus is to be erected. As I have elsewhere shown, the several species arise out of the incidence, in the subjects of this condition, of diverse excitants and local determinants.

affected. Sometimes, however, it extends quite a distance along the limb, or is reflected to a distant point—most frequently, but not invariably, an articulation. Thus when the wrist is involved, the chief complaint may be of pain in the elbow, the upper arm or the shoulder—as a rule, of the same side, but sometimes of the other side—or even of substernal pain; or elbow pain may be associated with disturbed sensation in or around the mammary gland. The pain is variously described as burning, boring, stabbing, aching, or general soreness. It may be constant, remittent, or intermittent. Sometimes it is absent when the affected part is at rest and is experienced only upon active motion. In other cases it is aggravated even upon passive motion. In a few instances the most gentle touch induces exquisite agony. This is especially marked at times when the costochondral junction is affected.

Numbness and tingling ("pins and needles" sensation) are frequently experienced in the fingers and toes; not only when these are themselves swollen and discolored, but also when their appearance is normal and the chief incidence of the disorder is elsewhere. *Paræsthesiæ* of various kinds in any part of the body—thus in one patient always in the face and lips—most frequently, however, in the extremities—may be premonitory symptoms.

The skin of the affected part or of the limb at some distance from the joint to which the pain is referred may be *discolored*. It is usually reddened; sometimes cyanotic, mottled, or pale and glistening; occasionally the seat of a papular, vesicular, or bullous eruption. Sometimes, however, there is no change of tint beyond that attributable to the distention. At other times there may be very slight and circumscribed swelling, but extensive reddish or purplish discoloration. The discoloration may be persistent. Ordinarily, however, it can be markedly lessened by gentle stroking in the direction of the venous current, or by elevation of the limb. When a terminal phalangeal joint is affected there may be ulceration at a nail margin. There may also be general or localized *erythemia* of face, trunk, or extremities.

Subjective *heat* in the affected part is common; but objective heat of a corresponding degree, or even sufficient to be detected by the touch of a normal hand, is relatively infrequent.

Fever is not common. When present it may be continuous, recurrent, or intermittent. It may show only as a rise of temperature, or there may also be headache, malaise, lassitude, and other constitutional disturbances. Headache or malaise or both may exist without elevation of temperature. In some persons there is both rise of temperature and constitutional disturbance, in every attack. In some there is rise of temperature only; in others, headache only. In some the pyrexia is preceded or followed or punctuated by chills or chilly sensations; or there may be chilly sensations without temperature change. In others there is never any febrile movement whatever; while still others may have fever in one attack and none in the next.

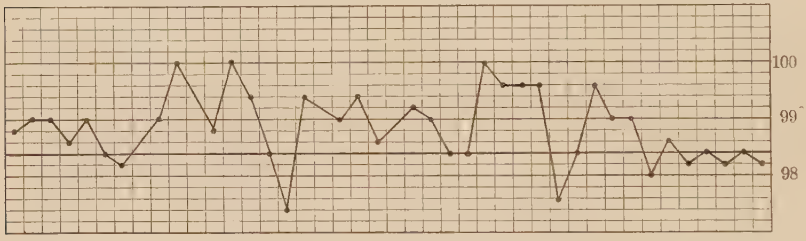

CHART 1.—"Capricious" temperature curve in a case of febrile polyarthrosis of between two and three weeks' duration.

In febrile cases the *temperature curve* is either entirely capricious, —rising and falling without rhythm or apparent reason (Chart I) —or shows a curious tendency to what may be termed an irregular periodicity. Perhaps this might better be described as paroxysmal. As a rule, the temperature rises suddenly and falls suddenly, when uninfluenced by treatment. (The times I saw it fall gradually, I thought that treatment might be responsible.) The height varies. Ordinarily it is moderate, between 101.5° and 103° F. I have seen it reach 104.4° F.; and I have also seen it keep below 100° F. The time of maintained height may be a few hours or a few days, rarely a week. In most cases the temperature falls to the normal line, or to a point slightly above or below the normal line, in from 12 to 72 hours. Recovery may then ensue shortly, or after a week or two, without further temperature rise. If the case be prolonged, however, the

curve tends to remain low, with slight fluctuations, for a variable time —from a day or two to a week or more—and then again rises abruptly, and remains high, or with a sharp up-and-down movement, for two or three days or more, to subside as suddenly as it rose. This may be repeated several times in the course of a long attack; but in only one case did I observe an approximation to regularity in the periods either of intermission or of relapse. In that instance the free periods were five or seven days, and the febrile periods three or five days. There were four of the latter, the entire attack lasting about six weeks (Chart II). One would be inclined to separate the prolonged febrile cases from the afebrile and brief cases, did not the same patient exhibit at different times, both forms—and still other varieties.

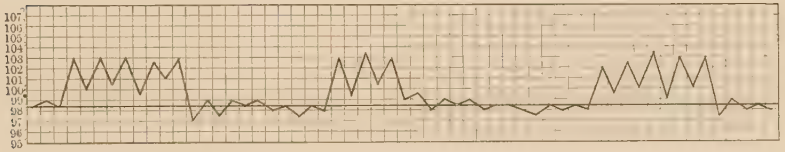

CHART 2.—Portion of temperature chart from case of polyarthrosis showing irregular periodicity. The portion of chart reproduced shows two febrile periods of five days and one of three days, with one afebrile interval of five days, one of seven days, and portion of a third which was also of seven days.

Apart from the symptoms, the chief factors of the morbid complexus are *duration*, *recurrence*, *extent*, and *distribution* (or time and space).

The *duration* of a particular attack may be brief or prolonged —from a few hours to many weeks. It may be continuous, remittent, or intermittent.

Recurrence may be periodic or irregular, at short or long intervals —from days or weeks to months or years. Thus the patient may have four or five attacks every year, for two or three or more years; and then perhaps be entirely free for five or even ten or more years. Or daily or weekly brief attacks may continue for months, and freedom suddenly ensue, to be maintained for a few months or for several years In this respect the condition parallels the more familar angioneuroses of the skin and mucous membranes—

urticaria, asthma,* lingual and laryngotracheal (angioneurotic) edema, etc.

Extent may be slight or great; *distribution* constant or variable. In most of the cases of "hydrops articulorum intermittens" upon record, a single joint, and always the same joint, was affected in the recurrent attacks—in the majority of instances, a knee. In the slighter forms to which I desire to direct particular attention, and especially in those which involve rather the soft tissues about the joints than the articular structures, several joints may be affected simultaneously or in succession. A single finger-joint or a single toe-joint may indeed suffer, but this is comparatively uncommon. Recurrences may affect the same joint or group of joints, or different groups. No joint in the body is immune. I have seen three cases affecting the spine or overlying soft parts, at least two cases affecting the temporomaxillary articulation, and one case of cricoarytenoid involvement.

The disorder is probably much more frequent than anyone has hitherto suspected. When I made my first special report upon the subject of articular and periarticular angioneuroses to the College of Physicians of Philadelphia† about two and a half years ago, I selected only six cases from records extending over twenty years, as instances which I then felt prepared to defend against sceptical criticism. Since I have studied the subject more closely I am convinced that I might have reported from those same records many times that number; but when one misses the opportunity to see the recurrences and is compelled to depend upon the imperfect sort of history obtainable from the average unobservant person, perhaps a judicious conservatism is not out of place. I am able, however, to add 21 new cases, making in all 27, distributed as follows as regards sex, age, fever, recurrences, and parts affected:

Sex. Males, 12 (44.5 per cent.); females, 15 (55.5 per cent.).

Age. Less than twelve years, 8 (29.6 per cent.); between twelve and twenty-five years, 12 (44.5 per cent.); between twenty-

* In hay fever and associated asthma the regular annual or other periodicity depends upon the regular annual (or other periodic) recurrence of the exciting noxa or noxæ. That is a different matter.

† Trans. Coll. Phys., Philadelphia, 1911, vol. xxxiii, series iii, p. 309.

five and fifty years, 5 (18.5 per cent.); between fifty and seventy years, 2 (7.4 per cent.).

Attacks. Observed in one attack (or series*) only, 13 (49.5 per cent.). Observed in several attacks (or series) 14 (50.5 per cent.). Total number of attacks (or series) observed in or reported by 27 persons, 110.

Fever. Febrile in all attacks, 5 (18.5 per cent.). Febrile in one or more attacks, but not in all, 6 (22.2 per cent.). Afebrile throughout, 16 (59.3 per cent.).

Parts Affected. Joints only, 3 (11.1 per cent.). Soft tissues only, 8 (29.6 per cent.). Joints and soft tissues, 16 (59.3 per cent.).

Distribution. Multiple in several attacks, 16 (59.3 per cent.). Multiple in one attack only, 3 (11.1 per cent.). Mono-articular in all attacks, 8 (29.6 per cent.).

Intra-articular Affections.† Spine: cervicoöccipital, 1. Face: temporomaxillary, 2. Extremities: wrist, 6; knee, 3.

Intra- and Peri-articular Affections.† Crico-arytenoid,‡ 1; temporomaxillary, 1; lumbosacral, 1; sternoclavicular, 3; chondrosternal, 2; vertebrocostal, 4; shoulder, 5; elbow, 10; wrist, 14. Hand and fingers: metacarpophalangeal, 14; interphalangeal, 16; hip, 1; knee, 9; ankle, 8; heel, 4; toes: metatarsophalangeal, 6; interphalangeal, 3.

Peri-articular Affections.† Acromioclavicular, 1; shoulder, posteriorly, 1; hand and fingers, 10; foot and toes, 6; wrist, 7; lumbosacral junction, 2; costochondral junction,¶ 4.

The foregoing figures are given more to accord with conventional methods of reporting than because I attach any great significance to them. The total number of individuals is too small, and too many accidental factors enter into the statistics, to permit this.

Thus as regards age, for example, it so happens that I saw

* Case I illustrates what is meant by a *series;* it is, of course, several brief attacks with short intervals, but to record it as twenty or more attacks seems inappropriate.

† These figures are not comparable with any others in the present records, since they include both multiple and mono-articular attacks and recurrences in cases in which different joints and groups of joints were involved each time, or in which at one time joints only, at another time soft tissues also, were affected.

‡ Laryngoscopic appearance.

¶ Probably periosteal edema. I have also seen several cases of periosteal edema at a distance from joints, which are not included in the present paper.

certain persons in childhood, others in adolescence, middle life, advanced age. Yet I feel sure that in a much larger proportion than indicated, the disorder manifests itself before the twentieth year, perhaps before the twelfth year. Ordinarily, however, it is not recognized. The present report gives, therefore, only the ages at which the patients were first seen by a certain observer. Again, however confident I may be that the history frequently given, of previous attacks of "rheumatism" or "gout" (not seen by me) really refer to the condition under discussion, I have felt justified in so recording those attacks in only about one-third of the instances. An error of judgment here, whether of omission or of commission, necessarily affects the statistics of fever, of recurrence, and of distribution. There is also a possibility of error in the anatomical diagnosis in the exclusion or inclusion of intra-articular effusion in the mixed cases.

CASE REPORTS

Case reports sometimes convey a more vivid picture than a general description with its necessary qualifications; but in a disorder so multifarious in aspect as that under consideration, reports *in extenso* are out of the question.

From the twenty-seven cases, however, some seven may be selected for brief narration, as illustrative at once of the great variety in detail of the morbid pictures and their essential sameness in fundamentals.

Case I.—*Intermittent, afebrile swelling of hands and wrist, with pain in upper arm; daily paroxysms in each series; monthly recurrence of series.* Ethel X., schoolgirl, aged thirteen years, complains of paroxysmal attacks of pain and swelling in the hands, with pain in the upper part of the arm. The trouble began two years ago. It usually affects one side only—and more frequently the right—but occasionally is bilateral. The swelling occupies the palmar surface, affecting chiefly the metacarpal-phalangeal articulations and overlying parts, including the hypothenar eminence. The dorsum is not involved. Occasionally the process extends to the wrist, which it encircles. Whether from pain or mechanical obstruction by the swelling, or both, it is impossible to close the hand. The affected parts are discolored (mottled red and purple) and swollen. They are subjectively, but not objectively, hot and are not especially tender to pressure

unless it produces passive motion. There is no fever. Sometimes there is pain in the thigh, and also (but rarely) in the foot as well. Swelling or discoloration, however, has not been observed in the lower extremity. The attack lasts from one to twelve hours. If prolonged beyond an hour or two, there will be remissions or intermissions. The paroxysm may occur daily, though not always at the same hour, for three or four days in succession. Until recently, there would then be a period of freedom of a month or more; but now the free interval is seldom longer than a week.

The child has not yet menstruated. She shows quick, hyperemic dermography, has typical tricolored nails, and exhibits slight retraction of the upper lids upon fixation of the eyes in convergence (Cohen's eye-sign). There is no tremulousness of the lids, and no lagging. The girl becomes car-sick easily and vomits, but never has sick headache. At times she has bilateral, temporal headache. She perspires readily, even in cold weather. During a paroxysm of pain and swelling the palmar surfaces perspire freely. They are purple or mottled at that time, while the dorsum of the hand, and the wrist, even if swollen, are red. The girl thinks the attacks are more frequent in cold weather; nevertheless she prefers winter to summer, as she becomes faint and is drenched with sweat on slight exertion in warm weather. There is no discoloration except during the attacks of pain and swelling. There is no lesion of the heart and no palpitation. The thyroid is not enlarged. The blood pressure is 110 systolic, 75 diastolic. The bowels are usually constipated. The urine shows an occasional trace of albumin, following an attack.

The *mother* of this patient is aged forty-four years. Three months ago she was subjected to a vaginal hysterectomy for myoma. She now complains of puffing of the fingers at night, with pain, which subsides during the day. This was preceded by similar pain and swelling in the left breast, which, however, came during the day and disappeared at night. She was seen but once, and at that time the hands were red and slightly swollen, the color running out and the swelling tending to disappear, upon elevation. The urine showed neither albumin nor sugar. She is a typical subject of *autonomic ataxia*.

The elder sister of the patient (also a typical *autonomic ataxia* subject), aged nineteen years, began to sneeze and present a hay-fever picture shortly after the family removed from Philadelphia to the interior of New Jersey. This, however, was in October, and the attack subsided in a short time. It recurred in June and lasted until she went to New York City in July, when it ceased after two or three days, but returned when she came home in September. It was ascertained that this girl was susceptible to "ivy" poisoning, and that there was considerable "poison ivy"* near the

* Identification of the noxa is not certain. The father was told to bring me a leaf but did not do so.

house. When this was cut down, the sneezing and associated symptoms ceased. Curiously, the younger girl who exhibited the angioneural arthrosis and dermatosis was immune toward "ivy."

Two maternal uncles have asthma, and one of these has had attacks of giant urticaria. On the father's side there is nothing significant.

Case II.—*Afebrile, paroxysmal, intermittent joint pain, in fingers chiefly, of brief duration, at first recurring fortnightly or monthly; later assuming nightly periodicity, with redness and swelling; later becoming premenstrual and associated with chilly sensations and blueness of the extremities.*

Mrs. X., aged twenty-eight years, housewife, has been married six years and is the mother of two healthy children, the youngest of whom is two and a half years of age and has been weaned for a year. The chief complaint is of pain in the joints, principally those of the fingers, which at the time of examination are tender and swollen and have been so, off and on, for two days. The left hand only is affected at this time. All the metacarpophalangeal joints and the first interphalangeal joints of the first, second, and third fingers are involved, together with the overlying tissues. The soft parts of the dorsum of the hand and wrist are also red, tender, and swollen. The patient states that the pain first appeared some time during her first pregnancy, coming on without warning, and lasting, with intermissions of an hour or two, for a couple of days, after which she was free for a fortnight, when it recurred in the same way. After that it continued to recur paroxysmally, fortnightly or monthly, without apparent definite relation to the menses. This pain is described as a dull ache, with occasional sharp exacerbations. At first it did not keep her awake. The hands and fingers were tender to the touch, but at this time were not red nor swollen nor hot. The trouble continued, despite treatment, until some time during the second lactation, when it became much worse and assumed new features. The pain would come on shortly after 6 P.M. daily and last until she fell asleep, frequently waking her during the night. At this time, also, swellings began to appear, at first occasionally, then with each recurrence of pain. The pain and swelling affected principally the knuckles and phalanges, but also at times the wrists, the knees, and the ankles. The toes were never involved. The two sides of the body were rarely affected at one time, but the hand and knee, or the knee and ankle of either side, might be painful or swollen in coincidence or in quick sequence. Sometimes a hard lump would develop on the hand or arm, at some distance from the joint, or a bruise-like patch would appear; or there might be both swelling and discoloration. The swelling did not pit upon light pressure. The spot was never red, nor did it have a red areola, nor was there any itching, but it was always tender to pressure. At no time was there fever, but there had been gradual loss of appetite and wasting. Treatment with baths and massage seemed to aggravate rather than relieve. Suddenly a period of freedom ensued, which lasted

for several months. During the summer preceding her visit to me, the patient had felt entirely well, and had regained flesh to within a few pounds of her former weight. About three months before she consulted me the trouble had returned, but again with a different aspect. This new series of phenomena would come on three or four days before the menstrual period, and would be relieved with the appearance of the menses. It would begin with general chilliness, the feet would become "cold as ice," the hands and ears blue, but not cold. The tip of the nose would become blue or white. After a few hours the finger-joints would become stiff and painful, then red and swollen; at times hot. With this, the cyanosis would disappear; but the feet remained cold. There had been but three such attacks. In the first, both hands had been involved at once for four days; in the second, the right hand for two days and the left for two days; the third attack was the one I saw. The left hand only was involved for two days. The next day the patient complained of pain in the throat, with difficulty of phonation. Laryngoscopic examination showed swelling and redness of the right vocal band and arytenoid eminence, which subsided in great part under a spray of epinephrin solution.

This patient presents the typical dermographic, ocular, and nail-bed signs of *autonomic ataxia*. She is not hysterical, but is easily startled. Among the other life-long phenomena of vascular imbalance is a tendency to perspire, even in cold weather, and paroxysmal, apparently causeless flushing of the face and ears, with "pins and needles" sensation in the lips and ears, sometimes in the extremities. The hands frequently become blue or mottled on going out of doors in cold weather. There is slight enlargement of the thyroid gland. There is pain on pressure, both in the supraorbital and infraorbital notches. There is no heart, lung, or kidney lesion. Information concerning other members of the family is lacking, except that the mother suffered with menstrual migraine and one sister died of pulmonary tuberculosis.

Case III.—*Recurrent monoarticular swelling of the knee; afebrile.* A. C., male, insurance agent, aged forty-one years; has had recurrent swelling of the right knee, without spontaneous pain or fever, for two years. It comes and goes suddenly without apparent reason. The swelling is evidently intra-articular; the patella floats. There is no redness, no tenderness, no heat. The attacks last from a day or two to a week, disappearing more quickly if the patient rests. There is pain upon motion only. The intervals of freedom vary from four to six weeks. The patient exhibits the signs of *autonomic ataxia*. He is of a gouty family and has had urticaria repeatedly. He has never had rheumatic fever or polyarthritis of any kind. There is no history of gonorrhea or syphilis. The patient recalls no injury to the part. There is no cardiac or renal disease. There is considerable susceptibility to drugs, especially salicylates, quinine, and iodides.

Case IV.—*Recurrent, intermittent polyarthrosis, with coincident edema of soft parts; febrile manifestations.* Mrs. L., aged thirty-eight years, housewife, has been under my care for twenty years, and during that time has exhibited many and various syndromes of vasomotor disturbance (including many so-called "drug and food idiosyncrasies"—anaphylaxis?). Also her mother, brother, sisters and children exhibit the same sort of susceptibilities. During my absence from the city in 1905, she was treated for what was called "articular rheumatism" by a physician unacquainted with her constitutional characteristics and tendencies. Since that time she has frequently had attacks of pain and swelling, sometimes affecting one joint, sometimes a group of joints, and occasionally exhibiting tenderness and redness, but never heat, of the overlying soft parts. These phenomena have usually been transient, lasting an hour or two, or at most twelve hours, but sometimes continuing for two or three days with or without intermissions. No periodicity can be traced in the recurrences; these being, as a rule, coincident with emotional disturbances—"servant troubles," sickness of husband or children, etc.—or with fatigue from zealous housecleaning, or prolonged dancing or "bridge," etc. Occasionally the attack has followed some dietary indiscretion. In the fall of 1910, following the prolonged incidence of measles and whooping cough among her children, during which time she had little rest, the patient complained of great pain in the left wrist, which was swollen, red, and tender, but not hot. She was anemic and weak, and was ordered to bed, but did not go. The next day, both wrists and the fingers of the left hand were involved, and there was fever (103° F.). This is the case giving the curious temperature curve shown in Chart II. The pain and swelling in the joints continued with periods of exacerbation and remission for six weeks. The last period of high temperature (there were four in all) ended in the fifth week. No connection could be traced between increase of temperature and aggravation of local phenomena, for the joints might be painful and swollen when the temperature was low or when it was high—and conversely. During the course of the attack, both wrists, both elbows, the fingers of the left hand, the toes of both feet, the right ankle and the right knee were involved; the wrists almost continuously, the other joints intermittently. Tingling in a part often preceded the swelling by twenty-four hours. At first there was considerable spontaneous pain in the affected joints; but for the most part the pain lessened or disappeared the day after the swelling developed, and would remain absent except upon active or passive motion or pressure, when it became, at times, very severe. During and after convalescence, pins and needles sensations in one or another extremity or in the rectum were frequently complained of.

Case V.—*Recurrent, afebrile, monodigital swelling and pain, associated with a bullous eruption, occurring in a gouty subject.* Mr. P. S., manufacturer, aged fifty-five years, belongs on the paternal side to a gouty family and has

had several attacks, both in hands and feet, of what was diagnosticated as gout by his former attendants. I have not seen him in a true gouty attack in the five years that he has been under my care. His finger joints are more or less thickened, but they have not become swollen or tender, except in the following manner. One finger—usually, but not invariably, the left index finger—begins to tingle and changes color. Ordinarily it becomes paler than normal, but sometimes it takes on a purplish hue. Pain now develops. The first joint swells, the skin reddens, and the swelling gradually spreads until nearly the whole finger is involved. The pain subsides. A number of small transparent vesicles appear, which apparently coalesce into fair-sized bullæ. These dry up, as a rule, without rupture unless the finger receives an inadvertent knock, in which case they may break, exuding colorless, odorless, unirritating fluid. The swelling subsides, the color disappears, and in the course of a week the finger has resumed its former condition. These attacks recur irregularly, there having been six in five years, but with one free interval of nearly three years. There is no organic disease; no recent gonorrheal infection; no evidence of persistent infection; no history of lues. The attacks have sometimes seemed to be provoked by indiscretions in diet. The patient, one son and one daughter, present the signs of vascular imbalance. The daughter recovered some ten years ago, under my care, from pulmonary tuberculosis, which exists in the patient's family on the maternal side.

Case VI.—*Intermittent and sometimes painful swelling of soft parts about gouty finger-joints, about acromioclavicular articulation, and along trapezius border and spine of scapula; occasional fever.* Mrs. R., aged seventy years, has a life-long history of gouty and nervous symptoms of various kinds. Her finger-joints are enlarged, often painful, and some of the fingers stiffened. She is subject to sudden burning and itching in the throat, accompanied with intense redness of the mucous membrane of the palate or pharynx, and subsiding in from ten to thirty minutes, or at most an hour. The sublingual veins swell suddenly and as suddenly return to their usual state. There are numerous little venous nodules along the right border and inferior surface of the tongue. The left pupil is ordinarily dilated, but at times suddenly returns to the normal size, or may be contracted. There is excessive retraction of the upper eyelids not only upon convergence, but also spontaneously during the excitement of interesting conversation. Dermographism is readily produced upon the patient's smooth, white skin. At times during the past ten years or more the soft parts over one or more of the gouty finger-joints swell. As a rule, the swelling is painless—but occasionally there is pain and redness. This may last for a day, or intermittently for a week. It may recur frequently, or after an interval of many months. More recently there are sudden seizures of intense pain in the upper left arm, followed by swelling along different portions of the neck and shoulder, most frequently over the acromio-

clavicular junction, or along the outer border of the trapezius, or above the spine of the scapula. These may be painful and are always tender, but never reddened. They appear suddenly, and ordinarily subside in from twenty-four to seventy-two hours. Sometimes they may last, with remissions, the better part of a week. There is no evidence of neuritis. There are no symptoms of angina. Six such attacks have occurred in two years, the first four within six months. Two of them were associated with slight fever. The first attack was attributed by the patient to "cold." She is careful in diet, and the bowels are regular. While there are periods of indigestion, and also periods of increased and diminished uric acid and urate output, no connection can be established between these and the swellings referred to. There is exophthalmic goitre and epilepsy in the mother's family; cancer and apoplexy in the father's family. The patient's blood-vessels are unusually soft for her years, and she has no disease of the viscera.

Case VII.—*Afebrile, recurrent joint pain associated with numbness under left breast and with nausea.* Mrs. G., aged twenty-five years, has been feeling badly for six years. She has attacks of palpitation; frequent sick headache; constipation; at times, paroxysmal dyspnea. She cannot eat strawberries, as this provokes hives. During the last year there have occurred "spells" of intense pain in the left elbow, aggravated upon motion. The pain lessens after half an hour or so, but does not disappear entirely for several hours. There is no swelling, tenderness, heat, or redness. The pain is preceded by tingling and numbness in the left ear, and followed or accompanied by numbness and stabbing pains under the left breast. With this last comes a feeling of faintness and nausea, but without vomiting, nor does the provocation of vomiting relieve it. There is no fever. The spells may come daily for several days, and then disappear for weeks. They bear no ascertainable relation to menstruation or constipation or other symptom, directly or inversely. There is no evidence of any organic disease whatever; no history of gonorrhea or syphilis. The patient shows the dermographic, ocular, and nail signs of *vasomotor ataxia;* the thyroid is not enlarged; there are numerous petechiæ and telangiectases on the body; pilomotor reflex is marked; she bruises easily and formerly bled from the nose. Glasses seem to have lessened the frequency of the headaches, which now occur only at the menstrual time, and not with every period. Four years ago the patient was operated on for appendicitis. The family history is not obtainable.

From what has been said, and from the histories given, both the difficulty and the ease of *diagnosis* should be evident. To mistake the condition for gout, rheumatism, muscular rheumatism, myalgia, neuralgia, neuritis, etc., is common, and is, indeed, excusable, so

long as one's attention has not been directed to the subject; and the subject is ignored by most text-books and systematic writers. In members of gouty and rheumatic families and in hysterical subjects the discrimination may be peculiarly difficult—and just such persons yield the majority of the cases. I have elsewhere[1] discussed this relationship, as well as that of hysteria, neurasthenia, tuberculosis, cancer, diabetes, and epilepsy, to autonomic disorders in general.

In *afebrile* cases the chief elements in diagnosis are the recurrent tendencies of the disorder, the family and personal history, and the characteristic signs of constitutional peculiarity[2] (idiosyncrasy) exhibited by the patient.

In *febrile* cases, the discrimination from rheumatic fever is at first difficult. A knowledge of the patient and his family helps, but may also lead astray, since a subject of autonomic ataxia is as liable as any other person to rheumatic infection. In the absence of authoritative bacteriologic, sereologic, or other exact tests for infective polyarthritis, the diagnosis becomes evident only as the case proceeds. It must be based on all the phenomena, not on any one point. A chief point of reliance may be the temperature curve which, as pointed out, may be utterly capricious or exhibit certain more or less well-defined phases, or even an apparent periodicity. Marked increase of eosinophiles or a disproportionately low count of polymorphonuclear leukocytes, or a marked excess of urinary indican or ethereal sulphates favors the diagnosis of angioneural disturbance, but is not conclusive. Nor are any of the reverse conditions conclusive negatively.

Some patients cannot bear salicylates, and, as a rule, these compounds, even when well borne, are less efficacious in relieving pain than in true rheumatism. They are not, however, entirely devoid of palliative effect, and hence a conclusive "therapeutic test" is not available.

The result of medication may be taken into consideration with other evidence—that is all.

Treatment must be individualized. It is more efficacious in prolonging the intervals of freedom and perhaps finally overcoming the tendency to recurrence, than in controlling—except

palliatively—the special attack or series of paroxysms. Indeed, its influence over the special attack is hard to estimate.

During the *acute stage* the chief elements of treatment are rest (local and sometimes general), regulation of diet,* elimination, and (relative) antisepsis. In some cases, special medication (and local applications) of a symptomatic and palliative character may be needed.

During *convalescence* from prolonged febrile cases the administration of roborants and hematinics is desirable.

During the *intervals of freedom* treatment must be directed toward prevention. To this end, measures for reëducating the vascular reactions and for restoring the tone of the vasomotor centres must be instituted; and the special exciting and determining factors, intrinsic and extrinsic, of the individual case, must be sought out and avoided or combated. In addition to the carefully individualized regulation of life and diet, persistent elimination, antisepsis, applications of hot and cold water, sometimes massage and high frequency electric currents or discharges, and the administration of angiotaxic medicaments (including the preparations and products of the glands of internal secretion) are thus among the measures applicable.

To discuss these therapeutic expedients in detail is impossible within the limits of the present article. It may be said, however, that much can be accomplished by persistence in treatment along well thought-out lines and with measures and methods carefully adapted to all the circumstances of the individual case. This is capable not only of giving a considerable degree of relief, but sometimes seems to overcome, in great measure, the morbid tendencies.

* For the first day or two in the more severe cases, and especially in what seems likely to be a prolonged febrile attack, the diet should consist chiefly of skimmed milk or whey with hot water to which sodium chloride (0.1 per cent.) and sodium bicarbonate (0.2 to 0.4 per cent.), and perhaps a little lemon juice, may be added. Later, barley water, sour milk, pancreatized milk, "one-minute" eggs, junket, pancreatized gruels, etc., may be given; and still later, fresh fruit and green vegetables. Meat and fish should be avoided.

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THE ETIOLOGY AND PATHOGENESIS OF BRONCHIECTASIS

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Since the young French student Cayol first called the attention of his preceptor, Laennec,[1] to a bronchiectatic lung, many theories have been advanced as to the etiology and pathogenesis of this interesting condition. Clinically it is rare, though relatively common in the autopsy-room in association with phthisis, as is pointed out by Fowler.[2]

We are, therefore, rather fortunate in being able to report 4 cases which occurred among 967 medical admissions to the University Hospital: 3 of them were under twenty years of age and 1 over forty. In Lebert's series of 83 cases, 47 per cent. occurred before and 53 per cent. after the fortieth year, while in Acland's series of 60 the percentages were 77 and 23 respectively. The predominance of the male sex must be largely due to the greater number of male admissions to the general hospitals from which the majority of the reports are drawn.

Anatomical and clinical classifications have been advanced by almost every writer on the subject. The generally accepted anatomical one includes three groups: (1) A regular or cylindrical bronchiectasis, in which there is dilatation of the tubes toward the periphery of the lung, and (2) a fusiform type, in which, in addition to the above, there is a dilatation at the periphery resulting in a bulbous termination; (3) the globular or sacculated type, in which the dilatations are strictly terminal.

[1] De l'Auscultation Mediate, 1819, i, 123 (Brosson et Chaudé, Paris).
[2] Diseases of the Lungs, by J. K. Fowler and R. J. Godlee, 1898, 123 (Longmans, Green & Co., London).

Of the many clinical classifications, in our opinion that of Hoffmann[1] seems the most scientific. He recognizes four groups: (1) inflammatory, (2) vicarious, (3) congenital, and (4) atelectatic,

1. The inflammatory group comprises the vast majority of the cases, and is nearly always of the saccular type. Two main subdivisions can be made: one associated with stenosis, and the other, the "indurative bronchiectasis," in which a thickened membrane attaches the portion of the lung affected with the ectasis firmly to the thoracic wall.

2. Vicarious or substituted type, in which the dilatation is always cylindrical. "When a portion of the lung has become inaccessible to the air and its volume is reduced, the traction excited on the adjoining tissues during inspiration will cause them to make an attempt to fill the space." The powerful pull of the muscles which dilate the thorax and so act on the lungs will be unable to expand the impermeable portions, but will expand other ones. According to the position and circumstances, this may affect the alveoli or the bronchi, and thus arise vicarious emphysema and bronchiectasis; hence, the not infrequent association of the two conditions. The mucous membrane seems thinned like a serous membrane. No inflammatory processes take part in the disease; it is a true emphysema of the bronchi, but it has little or no importance clinically.

3. Congenital bronchiectasis was first described by Grawitz[2] and subsequently by Neisser.[3] Grawitz recognized three varieties: (*a*) A universal ectasia, in which there is a large common cavity with numerous recesses; (*b*) telangiectatic, in which only the smaller bronchi are attacked. These may be regarded as a malformation or as the result of some intra-uterine disease, as syphilis. The morbid process is usually confined to one lung, which may present a cyst with a central space branching into a peripheral set of intercommunicating secondary and tertiary cysts, with serous contents. (*c*) Grawitz described a third variety, with numerous separate cysts formed on the bronchi of the third and fourth order

[1] Diseases of the Bronchi, Lungs, and Pleuræ, 1903, 178; Nothnagel's Practice (W. B. Saunders & Co., Philadelphia and London). (Edited by J. H. Musser.)
[2] Archiv f. Path. Anat., Berlin, 1880, lxxxii, 217.
[3] Zeit. f. klin. Med., 1901, xlii, 88.

some communicating with the bronchial lumen and others closed. Goitre was found associated with this malformation. (*d*) Lastly, congenital bronchiectasis may be due to a dermoid growth invading a bronchus, as described by Cyril Ogle.[1] These congenital cases are comparatively rare, and have never been seen by the writer.

4. Atelectatic: Ewart[2] also speaks of the atelectatic variety of Heller, in which there is an abnormal growth of the bronchial cartilages, together with remnants of the unexpanded non-pigmented fetal lung tissue, with epithelium of the pavement variety.

Etiology. Let us first consider Fowler's classification of the various conditions, which may be responsible for the development of bronchiectasis.

A. *Intrinsic,* that is, conditions acting directly through the bronchi.

1. *Acute and Chronic Bronchitis.* Bronchial catarrh is regarded by the majority of writers as the chief and earliest etiological factor, The special action of the catarrh consists in the mechanical plugging of the bronchioles. Juergensen[3] believes that long-standing bronchial catarrh may under certain conditions produce a growth of the interstitial connective tissue of the lungs, which further favors the origin of bronchiectasis. In children the bronchiectasis may run a very acute course, and the finest bronchi may undergo dilatation, a condition termed bronchiectasis. It has been fully described by Fowler, Walter Carr,[4] and others in England, but has received scant attention in America. The isolation of the influenza bacillus by Leichenstern and M. Beck in Europe and by Lord[5] and Boggs[6] in this country, in a large proportion of cases of bronchiectasis suggests the important role played by influenzal bronchitis in the etiology of bronchietasis.

2. *Bronchial Stenosis.* Bronchial stenosis may result from (*a*) gumma of the bronchi; (*b*) tuberculosis; (*c*) the pressure of an aneurysm or a tumor; (*d*) a foreign body.

[1] Trans. Path. Soc., London, 1897, xlviii, 1909.
[2] Allbutt and Rolleston's System of Medicine, 1909, v, 127 (McMillan & Co.).
[3] Handbuch der speciellen Pathol. u. Therap., 1877, H. Ziemssen, Band v, i, 286 (Leipzig, F. C. W. Vogel).
[4] Practitioner, 1891, xlvi, 87.
[5] Boston Med. and Surg. Jour., 1902, cxlvii, 662; ibid., 1905, clii, 537 and 574.
[6] Amer. Jour. Med. Sci., 1905, cxxx, 902.

(*a*) The role of syphilis in bronchiectasis and other pulmonary diseases has been much underestimated since the days of Laennec, according to Bouchut and Dujol.[1] They refer to 5 cases of bronchiectasis of Laurent and Guerin, in all of which the Wassermann reaction was positive, and give in deatil one case of their own in which other syphilitic lesions coexisted. L. A. Conner,[2] in a critical review of syphilis of the trachea and bronchi, found among 56 autopsies dilatation of the trachea three times and dilatation of both bronchi in 9 cases. He asserts: "The surprising thing is not that they occasionally occurred but that they should have been found so infrequently. In not more than 20 per cent. of the cases of permanent stenosis did bronchiectasis occur." It seems evident, therefore, that the tracheal or bronchial stenosis is not the chief determining cause of the bronchiectasis found. "Much more potent factors are the changes occurring in the bronchial wall and in the adjacent lung tissue, by which the muscular and elastic tissue of the bronchi upon which their strength and resilience depend is replaced by inflammatory tissue." Osler and Gibson[3] speak of three pathological types of syphilitic bronchiectasis: (1) With an interstitial pneumonia of the lower lobes, adherence of the pleura with general dilatation of the bronchi and cavity formation; (2) cases with a large single cavity in the upper lobe, with smooth, thick walls; (3) cases which follow stenosis of the bronchus. In children certain cases run an acute course and reveal at autopsy a picture identical with that described by Grawitz as congenital bronchiectasis. While the "honey-comb" appearance of a bronchiectatic process limited to one lobe is usually due to syphilis, Weill and Gardere[4] have recently reported two cases in children of three and ten years respectively in which the honey-comb lung was due to tuberculosis. The important conclusion to be drawn from the above observations is that syphilis plays an important role in the etiology of bronchiectasis and should always be excluded in a given case.

[1] Rev. de Méd., 1912, xxxiii, 585.
[2] Amer. Jour. Med. Sci., 1903, cxxvi, 57.
[3] System of Syphilis (edited by D'Arcy Power and J. Keogh Murphy), 1909, III, 7 (London-Oxford Med. Pub.).
[4] Lyon Méd., 1912, cxviii, 1221.

(*b*) Tuberculosis: Tuberculous processes are so slow that the lung can accommodate itself to the altered conditions, though stenosis may occur as the result of erosion through the bronchial wall. Chevalier Jackson[1] has seen 6 cases illustrating this possibility. The following case belongs in all probability to this category:

Case I.—Pulmonary tuberculosis (?); bronchial stenosis; bronchiectasis. M. D., aged forty-five years; laborer. Admitted March 13, 1913. Not referred. Clinical No. 881. Complaint: "Spells of coughing."

The family history was negative for tuberculosis. The patient was a day laborer, and had worked much recently in dusty atmospheres, shovelling coal. He had used alcohol to excess for years. He admitted gonorrhea at thirty-two years, at which time he had a single sore on the penis, for which he took local treatment and one bottle of medicine, and never developed any secondaries. He denied absolutely ever having been sick in bed in the past twenty years, but finally admitted to having some cough, with slight amount of sputum, for the past ten or fifteen years. Ten years before the onset of the present illness he had a pleurisy of the left side, which lasted for a day or two. In October, 1912, during a paroxysm of coughing, something "seemed to break" in his chest, and the sputum for a day or so following was especially offensive.

The present illness dated from January 17, 1913, when, following a prolonged spree, he developed cough and sputum. The cough was paroxysmal in character, associated with change of posture, and was especially frequent in the early morning. The sputum was profuse, and was so offensive as to be noticed by his fellow-workmen. It was usually yellowish in character, but occasionally had been blood-streaked. Since the present onset the patient had had chills, fever, and night sweats, and, though not confined to bed, he had not been at work. The appetite had been good. He fell from an average weight of 155 pounds to 133 pounds.

Physical examination revealed a well-developed and fairly well-nourished man, with flushed face, due in part to cyanosis and in part to dilatation of the venules. There was also cyanosis of the ears, lips, and finger tips, but no clubbing, though slight incurvature of the nails. The breath was extremely offensive, and of the same odor as the sputum. The thorax was of the emphysematous type, with somewhat restricted expansion, but no apparent flattening or retraction. Litten's sign was present on both sides. The percussion note was hyperresonant, except in the lower left interscapular region and base, where it was distinctly dull. Over this area vocal fremitus was diminished, and the breath sounds enfeebled and accompanied by numerous medium moist rales and high piping sonor-

[1] Jour. Amer. Med. Assoc., 1912, lix, 1123.

ous and sibilant rales. The heart revealed a normal area of dulness without displacement. The sounds were loud, regular, and clear, and there was no special accentuation of either second sound. Pulse was 84, large, full, and regular in force and rhythm. Blood pressure, 108 mm. (Faught); vessel wall distinctly palpable. The abdomen was round and soft. The liver was pushed somewhat downward by the emphysematous lungs, so that the relative cardiac dulness reached 5 cm. below the costal border in the right parasternal line. The edge of the spleen could not be felt. Hemoglobin, 70 per cent. (Sahli); red cells, 4,700,000; white cells, 16,600. Differential count: polynuclears, 81 per cent.; lymphocytes, 15 per cent.; large mononuclears, 3 per cent.; transitionals, 1 per cent. Wassermann test was negative on two occasions. Von Pirquet test was positive. The urine contained very slight traces of albumin and an occasional hyaline and granular cast. The sputum varied from 165 to 300 c.c. in amount, and was yellow, purulent, separating into three layers, and having a distinctly sweetish, offensive odor; on one or two occasions it contained elastic tissue; repeated examinations, however, failed to reveal acid-fast bacilli. Cultures were negative for Bacillus influenzæ, but numerous staphylococci and streptococci could be isolated. The skiagram revealed in the lower left back a distinct shadow corresponding to the area of impairment (Fig. 1). There was no evidence of infiltration of either apex. The patient on admission was running a high, irregular fever, which persisted for some two or three weeks, and was associated with a progressive loss in weight. Hypodermic injections of guaiacol cleared up the offensive odor of the sputum, and the daily inhalations of creosote also for a time caused considerable improvement in the patient's well-being, though the amount of sputum remained excessive.

On April 23, on account of another exacerbation of fever, sweats, and chills, and increase in the area of dulness, an aspirating needle was introduced into the eighth left interspace in the scapular line. After considerable resistance was overcome the needle was steadily introduced into the lung substance, and though nothing could be aspirated into the Ricord syringe, after withdrawal of the needle a small particle of thick, yellowish pus was found in the needle, which, in smears, showed numbers of pus cells and many bacteria, diplococci, and small bacilli. On April 26 a second puncture in the ninth interspace closer to the vertebral line was performed, but with absolutely negative results, though on this occasion a needle with a still larger lumen was used. Another skiagram revealed a more definite shadow corresponding to the increased area of dulness.

Under local anesthesia, on May 2, Dr. L. W. Dean introduced a bronchoscope into the left bronchus. This revealed, fourteen and a half inches from the upper central incisor teeth, red granulation tissue and a cicatricial stenosis, which after some difficulty was eventually dilated, resulting in the evacuation of two ounces of foul, thick pus. The cavity was thoroughly

cleansed, with cocaine and adrenalin, and the walls carefully examined. The latter were covered with red granulations, but no trace of a foreign body could be found. The drainage afforded by this procedure was followed by a temporary improvement in the patient's condition. Before subsequent dilatation could be carried out the patient left the hospital without permission.

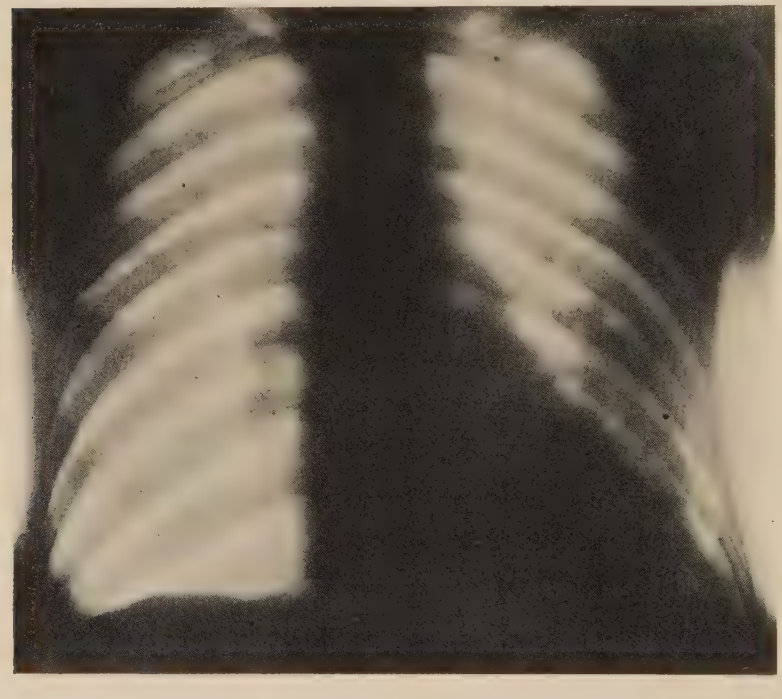

FIG. 1.—Case I. Pulmonary tuberculosis; bronchial stenosis; bronchiectasis.

(*c*) Many cases of thoracic aneurysm or mediastinal tumor exerting sufficient pressure on a main bronchus to bring about a certain degree of stenosis have been observed. In some of these cases bronchiectasis may result, as was frequently observed by Osler, who has termed it "aneurysmal phthisis."

(*d*) *Foreign Bodies.* The presence of a foreign body with parial obstruction of the bronchial lumen is not an infrequent cause. Cohn[1] found experimentally that dilatation usually occurs around

[1] Abhandl. d. Schles. Gesellsch. f. Vaterl. Kult. Phil. Hist. Abth. Bresl., 1862, Heft i, 71.

the foreign body and not behind it. It is the continual irritation that causes the inflammation and ulceration and leads to cavity formation. The local irritant acting continuously causes a peribronchitis which, extending from the site of the foreign body to the bronchi, favors in a special way the formation of bronchiectasis. Hoffmann states: "I must add that foreign bodies are too little considered as causes of bronchiectasis. We have cases enough in which the course and all the circumstances did not suggest the idea that a foreign body could have passed into the lungs and where the autopsy first showed to the astonishment of the physicians and friends what was the trouble; or the accidental expectoration of the foreign body established the diagnosis." Hoffmann believes that the stenotic form of bronchiectasis is of frequent occurrence, being present in many cases in which it is not recognized. Chevalier Jackson[1] urges the importance of considering each case of bronchiectasis as a possible foreign body one. "Of course, it is not known how frequently foreign bodies may be the cause of the bronchiectasis, but the similarity of the symptoms in bronchiectasis and in foreign bodies in the bronchi would certainly render exploratory bronchoscopy advisable even in a case with negative radiograph." The importance of this warning has recently come home to me, as the following case report will testify.

Case II.—Foreign body; bronchial stenosis, bronchiectasis. W. D., aged seven years; schoolboy. Referred by Dr. Mighell, Marshalltown, Iowa. September 25, 1911. Clinical No. 336. Complaint: "Cough and vomiting."

Family History. The family history was negative for tuberculosis.

Personal History. At the age of three he had lobar pneumonia, at five pertussis, and at six measles. Since the latter the patient had never been quite well.

Present illness began in February, 1911, with a severe cough occurring in paroxysms and associated with "vomiting" of large amounts of yellow, very offensive sputum. This might occur at any time during the day upon exertion or crying, but was more frequent and most abundant in the early morning. It was at times blood-streaked. The mother had noticed that the fingers were becoming short and stubby and that he was losing weight. A diagnosis of pulmonary tuberculosis was made by various physicians, and the sputum was examined repeatedly for tubercle bacilli,

[1] Loc. cit.

but with negative results. He first reported to the University Hospital in August, 1911, when he was examined by my associate, Dr. Van Epps, and a diagnosis of bronchiectasis made.

Physical examination on September 25 revealed a rather poorly nourished undersized boy weighing forty-one pounds. Face was pale. Definite clubbing of the terminal phalanges of both hands. The thorax was well-formed and symmetrical, but the right side moved less freely than the left. There was an area of definite dulness in the lower right back extending from the sixth dorsal spine to the base and from the posterior axillary fold to the spine. Over this area the breath sounds were amphoric and accompanied by numerous coarse moist rales. The left lung was clear on percussion, but revealed a few fine moist rales over the lower back. The heart showed no evidence of displacement or hypertrophy and the sounds were clear and of relative normal intensity. The pulse was 120, regular in force and rhythm, and of moderate volume. The abdomen was negative. On a subsequent examination the breath sounds over the dull area were suppressed, and it was noticed that these varied with the recentness of the paroxysm of the cough and expectoration. Hemoglobin, 60 per cent. (Sahli); red cells, 4,400,000; white cells, 21,000. The sputum was excessive, varying from 100 to 300 c.c. in the twenty-four hours; it was purulent, greenish in color, and settled into the characteristic three layers, and had an offensive odor. Microscopically on numerous examinations there were neither elastic tissue nor acid-fast bacilli, but great numbers of pus cells and diplococci, and occasionally some blood cells. A skiagram (Fig. 2) revealed a dense shadow corresponding to the dull area at the right base and merging with the right border of the heart.

He was given daily intratracheal injections of iodoform, with gradual amelioration in the amount of sputum and in the severity of the cough. During the last week of his stay in the hospital the amount varied between 20 and 140 c.c. in the twenty-four hours. As a precautionary measure, a day or two before discharge an aspirating needle was introduced into the right pleura and into the right lung, but no pus could be obtained. He was discharged on November 18, 1911, having gained six pounds in weight, and looking and feeling much better.

On December 12, 1912, Dr. R. F. French, of Marshalltown, Iowa, reported that the patient, during a fit of coughing, had brought up a tack which he remembered having swallowed in June, 1910, but which neither mother nor patient had thought of from that time. Upon receipt of this letter we immediately reëxamined the skiagram and found that we had overlooked the definite shadow of the tack lying head downward in one of the large bronchi of the right side. Dr. G. E. Hermence, who subsequently had charge of the patient, elicited the following new facts from the mother: She now remembered that the boy had swallowed the tack in June, 1910. At the time he had had a hard coughing spell, but recovered

and the tack was forgotten. In January, 1911, he began to cough, especially in the morning, and it was noticed that he raised a large amount of sputum and had distinct fever, as high as 104° on one occasion. Since his discharge from the University Hospital the intratracheal injections were continued until September, 1912, when they were stopped on account

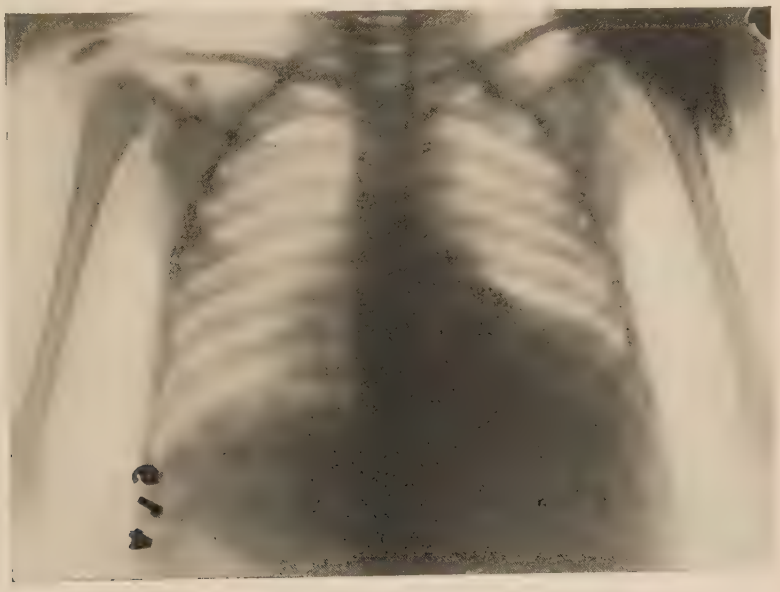

FIG. 2.—Case II. Foreign body; stenosis; bronchiectasis.

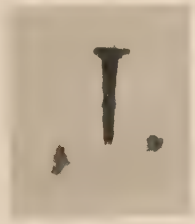

FIG. 3.—Tack expelled from bronchus by Case II. Note slight erosion of the head of shaft.

of local irritation of the throat. About September 1 he was worse again, and in one of the paroxysms something seemed to "break in his side," which was followed by an unusually large amount of yellowish, purulent material. In another violent paroxysm, on December 3, something seemed to choke him, and upon putting his finger into the pharynx he pulled out the tack (Fig. 3). Since then the patient has felt better. The cough and

sputum have gradually become less. A request for him to return to the hospital for examination was not granted, but Dr. Hermence, under date of April 24, 1913, reported that the cough and sputum have much lessened and that the latter has little or no odor. He had gained in weight, and now leads the normal life of a boy of his age. The physical examination still reveals an area of dulness at the original site.

Hoffmann calls attention to the probable frequent origin of bronchiectasis from inhalation of solid particles. It is of interest to note that Case I of our series assigned the recent exacerbation of the cough and expectoration to the inhalation of coal particles while working in a railroad coal chute.

The importance of bronchial stenosis in the etiology of bronchiectasis has been demonstrated experimentally by W. G. MacCallum[1] and his pupils W. L. Thorton and J. P. Pratt.[2] Bronchial stenosis was produced either by a screw clamp around a bronchus or by placing short pieces of tubes, with different sized lumens, inside of the bronchus. When one bronchus was partially occluded the pressure changes in the lung behind the occlusion were marked; the greater the occlusion the greater the negative pressure on inspiration, and the greater the positive pressure on expiration. In addition, inspiration and expiration were so protracted that the opportunity for a pause no longer existed, and they occupied the whole cycle. When the lumen of a bronchus was reduced the lung corresponding to the bronchus involved failed to contract during expiration as completely as the lung with an unobstructed bronchus. Owing to this failure to completely contract, an excess of air remained in the lung, which was consequently continually distended. What has been represented in these experiments as taking place rapidly must appear gradually in man as the result of a bronchial stenosis, due to the pressure of a tumor or some similar cause. If a foreign body be lodged in a bronchus the above changes must follow very rapidly. "The partial occlusion of a bronchus causes air to be entrapped and the bronchus to be distended, with greater changes in pressure behind the obstruction during respiration. In coughing and related processes the pressure inside the bronchus is greater than the pressure outside the bronchus only

[1] Bull. Johns Hopkins Hospital, 1908, xix, 215. [2] Ibid., 1908, xix, 230.

by the force of the elastic recoil of the lung; so there is no marked tendency on the part of the bronchi to undergo dilatation."

3. *Bronchial Obstruction.* According to Lichtheim[1] sudden and complete obstruction of a bronchus causes in twenty-four hours collapse of the lung area to which it is distributed with purulent accumulation within the tubes. This is followed by emphysema of the surrounding tissue and in several weeks by dilatation of the neighboring bronchus. Occlusion of the bronchus does not necessarily cause a bronchiectasis in the area of supply unless there is also an opportunity for the development of a purulent bronchitis; hence a stenosis is more favorable for its development than an absolute occlusion. This was well illustrated in a case reported by Sutherland,[2] in which the bronchial obstruction was due to the impaction of an O'Dwyer tube; at the autopsy the greater part of the lower lobe was destroyed by an abscess and the remaining portion was collapsed and airless; the surrounding smaller bronchi were dilated and embedded in soft friable lung tissue.

B. *Extrinsic*, that is, conditions acting indirectly through disease of the lungs or pleuræ.

1. *Pulmonary Changes.* (*a*) *Collapse of the Lung.* This exciting cause is common in the child as a result of capillary bronchitis or of bronchial stenosis, as has already been described.

(*b*) *Pneumonia.* Either the lobar or lobular variety is regarded by many as a common cause. It must be borne in mind that lobular pneumonia also frequently supervenes in a well-established bronchiectasis. (Compare Case III.)

(*c*) *Emphysema.* A moderate degree of bronchiectasis is usually found associated with old-standing cases of emphysema.

(*d*) *Fibrosis of the Lung.* Fibrosis of the lung, sometimes termed cirrhosis of the lung, may result from an unresolved or chronic pneumonia or from the fibrosis developing in certain cases of pulmonary tuberculosis. Ewart emphatically states that bronchiectasis (Rokitansky to the contrary) may occur in subjects of chronic phthisis; on the other hand, chronic bronchiectasis may end in tuberculosis, though this is a rare event.

[1] Archiv f. experimentelle Pathologie u. Pharmakologie, 1879, x, 54.
[2] Lancet, 1892, i, 189.

Hoffmann believes a tuberculosis establishing itself in the finer branches of the bronchi may lead to the formation of small bronchiectatic areas, which, however, do not produce clinical symptoms and are therefore not named in the clinical account of bronchiectasis. In many cases of so-called fibrous phthisis characteristic bronchiectasis occurs, and their course will indicate that the cicatricial contraction of the tissue was really the cause of the bronchial dilatation.

Syphilis in the form of bronchial gummata has already been referred to, but it must be mentioned that specific scar formation and infiltration of the parenchyma are especially favorable to the production of bronchiectasis.

2. *Pleural Changes.* Pleurisy with effusion, whether serous or purulent, will result in collapse of the lung; dilatation of the bronchi and chronic thickening of the interlobular and interalveolar connective-tissue may follow in the order named, or these changes may proceed together. Extensive pleuritic thickening at the base cripples the lung and the respiratory function may be entirely lost.

In a given case it is difficult if not impossible to state which one of these various extrinsic factors is responsible for the bronchiectasis. In fact they may all be present in any one case, and it is perhaps best to group those cases under the general term of "pleuropneumonic." The following histories are illustrative:

Case III.—Pleuropneumonic bronchiectasis. A. C., aged fourteen years; schoolgirl; white; American. Clinical No. 405. Admitted September 17, 1910. Referred by Dr. Post of Maquoketa. Complaints: "Cough and profuse expectoration."

Family History. Negative for tuberculosis or other lung trouble.

Personal History. Had chicken-pox and measles in early childhood. In 1903 she received an injury (?) to the back, from which she was confined to bed on account of pain, cough, and high fever.

Present illness began in December, 1907, with an attack of scarlet fever, complicated by severe pain in the left side. It was not known whether the patient had a pneumonia or a pleurisy at that time. For two years subsequently she suffered from a troublesome cough, but without sputum. About September, 1909, expectoration made its appearance. It was profuse, yellowish in color, and with an offensive odor, and at times blood-streaked. The cough became paroxysmal, occurring at intervals during

the day, but more particularly in the morning. She averaged about five or six attacks in the twenty-four hours. She did not notice any effect of posture. At times the sputum would fill a teacup. During the last two or three years the mother had noticed gradual enlargement of the finger tips, and a liability to chills, fever, and sweating. The patient had lost ten to twelve pounds in weight. There had been slight cyanosis.

Physical examination showed that the patient was still well-developed and nourished. Weight, eighty-four pounds. The finger tips were makedly clubbed and the nails incurved; there was also slight clubbing of the big toes, with incurvature of the nails, but no enlargement of the bones. The thorax was decidedly long and narrow, with a somewhat acute costal angle. The left upper front was flatter and moved less with respiration. The right lung was resonant, and except for somewhat harsh breath sounds in the second and third right interspaces and a few medium moist rales over the back was normal throughout. The left lung revealed an area of dulness beginning at the level of the fourth dorsal spine and extending to the base and outward to the midscapular line. Over this dull area the breath sounds were enfeebled, except after a paroxysm of coughing, when they became distinctly bronchial, and almost amphoric in character. Everywhere throughout the left lung, but particularly over the lower lobe, were heard numerous medium and large moist rales. There was no displacement of the heart, no evident enlargement of the right chamber, and no abnormality of the heart sounds. The sputum varied in amount from 410 to 200 c.c. in the twenty-four hours. It presented the characteristic three layers, had a greenish-yellow color, and a fetid, sweetish odor. It contained many pus cells, but daily examination failed to show the presence of elastic tissue or tubercle bacilli. The blood count on September 22 revealed hemoglobin, 80 per cent. (Tallquist); red blood cells, 5,060,000; white blood cells, 12,000. Differential count: Polynuclear, 75 per cent.; lymphocytes, 14 per cent.; large mononuclears, 10 per cent.; eosinophiles, 1 per cent. The von Pirquet test was negative on two occasions. The skiagram (Fig. 4) on September 17 revealed enlarged glands in the hylum of the right lung. On the left side below the cardiac shadow there was an abnormal opacity, 10 cm. in diameter, corresponding in position to the signs of the cavity on physical examination. On September 27 she was started on the intratracheal injections of iodoform. In addition she received general dietetic and hygienic supervision. With the exception of a sudden onset of chill, fever, pain in the left side, and the presence of a dry friction rub, due to an infection of the left pleura on October 24, 1910, and again on January 17, February 25, and February 28, 1911, the patient gradually and progressively gained in strength and weight, and the amount of sputum fell to about 75 to 100 c.c. in the twenty-four hours. On February 28 the patient coughed up 270 c.c. of fetid sputum, which suggested a temporary obstruction to the outflow of the cavity, though on this as on previous occasions

a friction rub was audible. On March 14, 1911, the white blood cells were 8000, and the polynuclears 88 per cent. On March 21 the patient was discharged, having gained twenty-four pounds in weight, and having only one or two paroxysms in the twenty-four hours. The sputum on the last day measured 60 c.c. The signs at the left base, however, remained unaltered. In the hope of finding a definite abscess cavity and draining the same by

FIG. 4.—Case III. Pleuropneumonic bronchiectasis.

surgical means, an aspirating needle was introduced into the ninth interspace in the back corresponding to the middle of the dull area, but no pus could be obtained.

A letter from the mother on March 25, 1913, reported that the patient weighed 125 pounds, which meant an additional gain of fourteen pounds since discharge. The cough and sputum, however, persisted.

Case IV.—Pleuropneumonic bronchiectasis. C. M., male, aged seventeen years; schoolboy. Referred by Dr. W. H. Spencer, of Cedar Rapids. Admitted October 27, 1910. Clinical No. 83. Complaint: "Stomach trouble." Father and mother, four brothers, and three sisters living and well. Tuberculosis on both paternal and maternal sides of family.

Personal History. Patient was born and bred in Iowa. He had measles and whooping cough in childhood, but denied pneumonia and pleurisy previous to the present illness. The mother stated that he had been subject to winter cough since his eleventh or twelfth year, associated with sputum. Average weight at fifteen years was 115 pounds.

The present illness dated from his fourteenth year, when he had an "abscess in the left side," since which he had never been strong. For the last three years he had practically a constant cough, associated with the expectoration of large amounts of greenish-yellow and offensive sputum, especially profuse in the early morning. At fifteen years he had several attacks of hemoptysis. He had dyspnea on exertion and fever until six months before admission. The appetite became poor, and he had lost steadily in weight. The sputum had been repeatedly examined for tubercle bacilli, but with negative results.

Physical examination revealed a tall, slim, delicate-looking youth of blond complexion. Weight, 107 pounds. There was dyspnea on the slight exertion of undressing. He was a mouth-breather. There was definite clubbing of the finger tips and well-marked incurvature of the nails, with slight cyanosis of the nail beds. The thorax was large, well-developed, and slightly asymmetrical in front, the left side being smaller than the right and expanding less. The left back seemed flatter than the right. The percussion note was everywhere resonant except in the lower left back, where it was impaired, though not actually dull. Over the impaired area tactile fremitus and vocal resonance were somewhat increased, while the breath sounds had a distant blowing, almost tubular quality. Over the entire left back there were numerous medium moist rales, with here and there a fine crepitant rale. The right lung was resonant throughout, while the breath sounds were vesicular except in the lower right axilla and right back from the angle of the scapula to the base, where they were distinctly harsh and accompanied by numerous medium moist rales and bronchophony. The heart was neither hypertrophied nor displaced. The heart sounds were clear at the apex, while at the base the pulmonic second sound was distinctly accentuated. The pulse varied from 90 to 112 to the minute, regular, of fair volume, and moderate tension. The abdomen was flat and soft, and neither liver nor spleen was palpable. The blood revealed hemoglobin, 53 per cent. (Sahli); red blood cells, 5,250,000; white blood cells, 15,600. Differential count. Polynuclears, 73 per cent.; lymphocytes, 24 per cent.; large mononuclears, 3 per cent. The urine was normal. The sputum varied in amount from 150 to 190 c.c.

in the twenty-four hours, and had a distinctly sweetish odor at times, but at others was offensive. Microscopically it was negative for acid-fast bacilli and elastic tissue on seven observations. The von Pirquet test proved negative. Temperature ranged between 98½° and 99½°. On October 27, 1910, a skiagram (Fig. 5) revealed a distinct shadow at the left base,

FIG. 5.—Case IV. Pleuropneumonic bronchiectasis.

merging with the heart dulness. There was also a slight increase in the normal shadow at the right hylum and a little opacity at the right base. The patient received a few intratracheal injections, after which he went home with directions to his physician to continue treatment. He was lost sight of, and a letter from Dr. Spencer on April 14, 1913, reported that he had died some two years after his discharge from the hospital.

Pathogenesis. The best *résumé* of the various theories of the production of bronchiectasis is given by T. Grainger Stewart and G. A. Gibson,[1] and will be adopted in this paper with some modifications and additions.

1. The mechanical pressure of the stagnating secretion was first suggested by Laennec and adopted by other French pathologists. According to this theory the accumulation of the mucus, aided to a certain extent by cough, causes the dilatation. But there is no special accumulation of mucus in some cases, and further, it is mechanically impossible when one considers the consistency of the secretion and the free outlet in two directions.

2. Concentrated air pressure is advocated by Raynaud, Williams, and others. The dilatation is explained as compensatory to atrophy or collapse of neighboring areas of the lung. Further, the pressure of the inspired air acts with greater force on the diminished respiratory surface. Against this theory are two facts: (1) Bronchiectasis arises without preëxisting cough, and cough is common while bronchiectasis is rare; (2) even if such a cause were present, emphysema rather than bronchial dilatation would result, for the bronchi are less yielding than the pulmonary tissue.

3. Extrabronchial traction was emphasized by Corrigan, Barth, and Hamilton. According to them dilatation resulted from traction upon the bronchial walls by the contracting cirrhous lung tissue aided by pleuritic adhesions to the chest wall. Against this speak the following facts: (*a*) Bronchiectasis often occurs without cirrhosis and without pleural adhesions; (*b*) the possibility to demonstrate that the dilatation may precede in some cases the condensation of the lung; (*c*) the process of traction could never explain the opening of the dilatations into one another nor the formation of bridges in the dilated portions: (*d*) cirrhosis of the lung does occur without bronchiectasis, the latter being present in only 30 per cent. of the former according to Bastian.

4. Inflammation of the bronchial wall was first advanced by Stokes and adopted by Wilson Fox among others. They pointed out that the bronchial wall, as the result of the inflammation, loses

[1] Twentieth Century Practice of Medicine, 1896, vi, 552 (New York, Wm. Wood & Co.).

its elasticity, contractility, and ciliary movement, the bronchi consequently dilate, and so an accumulation of secretion occurs. Yet if bronchitis leads to bronchiectasis, why is the former so common and the latter so rare? McPhedran[1] answers this by saying that "inflammation of the bronchi to be effective in causing dilatation must be destructive; it must destroy the structure which gives resisting power to the bronchial wall, namely, muscular tissue, elastic tissue, and cartilge." Another objection, however, is that bronchiectasis may develop without preëxisting bronchitis; and lastly, the walls of the dilatation are not infrequently found atrophied and without signs of inflammation.

5. Nervous theory: Lebert thought the loss of power of the bronchial walls was dependent rather more upon nervous influences than upon inflammation. Stewart and Gibson regard this theory as purely hypothetical and gratuitous, and point out that in analogous processes, as aneurysm, varicose veins, and staphyloma posticum, there is no reason to look for nervous causes but rather local nutritional changes.

6. Primary atrophy of the bronchial wall: This explanation of the origin of bronchiectasis was first advanced by Grainger Stewart in 1867, founded upon a series of pathological and clinical observations. In Stewart's opinion it offered a satisfactory explanation of the most important and commonest groups of cases which he terms primary, while he fully admits the existence of other secondary varieties. "The process then is to be regarded as analogous to the direct atrophic form of emphysema and not improbably to result from a constitutional, possibly an hereditary effect."[2] In primary bronchiectasis the essential element is an atrophy of the bronchial walls; the cause for such atrophy is not yet understood, but it is probably connected with constitutional peculiarities. The walls of the bronchi being so thinned and weakened, yield to the ordinary air pressure, or it may be that deep and sudden inspiration or violent muscular exercise or the sudden expiratory efforts made while the glottis is closed in the act of coughing aid in the process of dilatation. The existence of dilatation favors the accumulation

[1] Osler's System of Medicine, Oxford, 1908, iii, 681.
[2] Stewart and Gibson, loc. cit.

of mucus, and this in turn to inflammation and formation of villous processes, increased connective tissue, irritation of the cartilages, and to consolidation of the surrounding lung and pleuritic adhesions.

The secondary bronchiectasis may occur in the course of various morbid conditions of the surrounding lung tissue or be due to mechanical obstruction to the free passage of air in inspiration and expiration. The explanations of the pathogenesis of bronchiectasis advanced by most writers apply to these secondary cases: "How much influence to assign to each of these causes in any given case is difficult to determine."

7. Ewart's explanation: William Ewart[1] has pointed out that the common feature of all cases of bronchiectasis is faulty distribution of space between the air tubes and pulmonary tissue. Any excessive stress ultimately finds out the least resistant tissue, which is most often the pulmonary, and therefore becomes emphysematous; if, however, the bronchi are previously diseased they may suffer. In disease, therefore, other mechanical factors arise, namely: (1) Within the bronchi an accumulation of mucus and an antecedent or resulting degeneration of the bronchial wall; (2) changes induced in the lung tissue may bring about a faulty allotment in space, namely: (*a*) emphysema, much of which is effect, not cause, (*b*) collapse, which when occurring unevenly at one side of a bronchial tube may act as one of the agents of dilatation, (*c*) increase in the subpleural, perilobular, and interlobular stroma.

"As to the general mechanism of the dilatation we must again look for some elementary factor common to all varieties, and this we find in obstruction in the broadest sense of the word." Owing to the alternating direction of air currents an obstruction may lead to dilatation either on its proximal or on its distal side. The dilating force is usually not as in other tubes, as the alimentary tract, due to the pressure of an internal accumulation, but has its seat on the distal side of the dilatation; it is an aspirating not a forcing pressure. "The inspiratory traction made by the chest wall if it should fail to expand an obstructed lobule, might be transmitted to the delicate air tube adjoining the latter and might dilate it. Owing to the solidarity existing between all parts of the lung, this encroachment

[1] Loc. cit.

of bronchial space into the vacated pulmonary space may occur at a distance from the original collapse." The progressive increase in the dilatation may be brought about according to either the inspiratory or the expiratory hypothesis. In the former, according to Laennec, an abnormal inpiratory effort preceding cough throws a damaging stress upon the weakened parietes of the bronchial tube. The expiratory hypothesis has been advanced for bronchiectasis as for emphysema. In expiration with the glottis closed the pressure may rise to 80 mm. of mercury and in severe coughing to 110 mm. or more, while in quiet expiration it does not exceed 2 or 3 mm. During inspiration the air is sucked through the stenosis, but in expiration the expelling force is often insufficient, for the expelling force in this case is represented only by the elasticity of the tissue lying beyond the constriction. If a mass of mucus is present it may act like a valve, so that air can get in much more easily than it can get out. Stagnation of the air results, the pressure becomes very high, and remains so continuously. This is greatly assisted by attacks of coughing. Yet if we accept this we must answer the question, why it is that bronchiectasis and emphysema are not universal, inasmuch as we are daily subjecting our bronchial tree to an intense muscular strain with closed glottis. Evidently this immunity is dependent upon a perfect distribution of pressure in the healthy lung. Cough may be powerless to dislodge the secretion and yet propel it far enough to cut off the dilated alveolus from the main bronchus. The result of a recurring valvular obstruction of this kind would be not only continued fulness of the dilatation while the surrounding tissues are being relieved of much of their air, but a maintenance within it of the highest air pressure at the time when the air pressure in its vicinity is at its minimum. Hoping to obtain some light on this theory, I turned to the studies of Tendeloo on Emphysema.[1] In this I was disappointed, as there was nothing in these technical papers on the dynamics and statics of emphysema that I could find in any way applicable to the mechanism of bronchiectasis.

Ewart shows how cough, bronchial catarrh, interstitial pneu-

[1] Studien über die Ursachen der Lungenkrankheiten, 1902 (Wiesbaden, Bergmann); ibid., Ergeb. d. inner. med. u. Kinderheilk, 1910, vi, 1.

monia, pleuropneumonic fibrosis, and stenosis may each and all bring about an abnormal distribution of air space between the tubes and pulmonary tissue. It must be confessed that after due consideration of the various theories advanced it would seem that Ewart's hypothesis is the broadest and the most logical.

Conclusions. 1. Bronchiectasis is a not infrequent clinical condition, and is too often mistaken for pulmonary tuberculosis.

2. The possibility of a foreign body or syphilitic stenosis must always be excluded as etiological factors.

3. Skiagrams are helpful in the case of a foreign body, but bronchoscopy should be carried out to exclude a foreign body and to treat a possible stenosis of a bronchus.

4. The etiology is manifold, but the inflammatory causes are the most common.

5. Of the various theories, that advanced by William Ewart is the most rational and scientific. It considers a faulty distribution of air space as a predisposing factor common to all cases. The general mechanism of dilatation is found in obstruction in the broadest sense of the word.

DISCUSSION

Dr. F. T. Lord: The pathogenesis of bronchiectasis is always an interesting question. There are three theories: (1) A bronchial theory; (2) a pulmonary theory, and (3) a bronchopulmonary theory. From a series of autopsies in Boston certain suggestive clues have been found; I wish to mention one only. In one case it could be demonstrated that around the bronchiectatic cavity there was no evidence of involvement of pulmonary tissue at all. There had been some degenerative disturbance of the bronchial wall alone, capable of making the dilatation possible.

Dr. W. G. MacCallum: The importance of bronchial obstruction in the etiology of bronchiectasis is admitted, of course; but the statement that dilatation is produced by the expiratory pressure increase accompanying coughing with the glottis closed requires scrutiny. The idea that such pressure increase could be applied at any one point seems incon-

ceivable to me. An alternative explanation suggests itself. In cases of bronchial obstruction with stasis of secretion there is a certain obstruction to inspiration; but inspiration is accomplished by muscular action which will overcome the obstruction, while expiration being accomplished merely by the elastic recoil of the chest does not overcome the obstruction, so that there is a gradual imprisonment of air in the obstructed bronchus, with gradual increase of intrabronchial pressure until it is sufficient to overcome the obstruction. This localized increase of pressure being continued long enough will finally produce permanent dilatation of the bronchus.

Dr. J. A. Capps: The paper is a timely one; important because some of the recently advanced therapeutic measures have been disappointing. This is notably true of vaccine treatment, as might be expected in view of the mechanical changes underlying the whole condition.

Dr. W. G. MacCallum: It is obvious if a bronchus is obstructed, that the region ventilated by it will be in a state of negative pressure in inspiration; but this would render the region liable to compression rather than dilatation, when subjected to the force of an obstructed cough.

Dr. C. F. Hoover: From experience in measuring the ventilation of dogs' lungs with the Zundt apparatus, I have found that the negative pull may be measured when stenosis of either the inspiratory or expiratory tube is produced. With an expiratory stenosis the volume of the lung is increased.

Dr. Howard: Of all the theories as to the pathogenesis of bronchiectasis, that of Wm. Ewart is the most scientific, viz., a faulty distribution of air space caused by stricture of air tubes. The most important therapeutic suggestions are the search for foreign bodies by *x*-ray examination in every case of bronchiectasis; or, failing to find a foreign body, to employ the bronchoscope and seek to dilate strictures.

INDEX

Abbott, A. C., antityphoid vaccination in the army, 465, 467
Abel, J. J., removal of diffusible substances from the circulating blood by means of dialysis, 51
Abscess of liver following typhoid fever, 572
pulmonary, 302
Acidosis, diabetic, 469
Addis, T., urobilin, 617
Address of president, 1
Adherent pericardium and the operation of cardiolysis, 254
Anderson, J. F., serum anaphylaxis, 101
typhus fever in the United States, 81, 86
Angioneural arthroses, 739
Antityphoid vaccination in the army, 457
Auer, J., heart-beat in the dog, 545, 571

Bacterial endocarditis, 309
Baetjer, F. H., ulcer of stomach and duodenum, 157, 175
Barker, L. F., address of president, 1.
Bass, C. C., manner in which cerebral malaria is produced, 683
Benzol in treatment of leukemia, 202
Biggs, H. M., typhus fever in United States, 86
Billings, F., benzol in treatment of leukemia, 202, 224
epidemic poliomyelitis, 68
exophthalmic goitre, 604
Rigg's disease, 93
serum anaphylaxis, 100
Blackford, J. M., exophthalmic goitre, 595, 605
Bleeding in typhoid fever, 686
Boggs, T. R., multiple congenital osteochondromas, 248, 253
Bond, C. S., pneumonia, 616
Rigg's disease, 94
Bronchiectasis, 758
Bronchopneumonia, lobar form of, 430
Brooks, H., pulmonary osteoarthropathy, 275
Brown, L., pulmonary tuberculosis, 441, 448
Brown, P. K., primary infection with tubercle bacilli, 408, 421
pulmonary abscess, 308
Brown, T. R., fixation of stomach and intestines, 136, 156
Bunting, C. H., cultural results in Hodgkin's disease, 226

Cabot, R. C., benzol in treatment of leukemia, 224
bronchopneumonia, 439
exophthalmic goitre, 604
fixation of stomach and intestines, 156
hypersensitive cardiovascular disease, 385
lesions of the nervous system, 738
x-ray examinations, 50
Carcinoma, statistical study of, 235
Cardiovascular therapy, 490
Camac, C. N. B., dental sepsis, 700
Campbell, A. D., recurrent pneumonia, 422
Capps, J. A., bronchiectasis, 780
pneumonic hemiplegias, 489
venous blood-pressure, 490
Cerebral malaria, 683
Cerebrospinal nervous system, diagnosis of lesions of, 720
Christian, H. A., studies of experimental nephritis, 198, 201
Circulatory failure in diphtheria, 399
Cirrhosis of liver, 497
Cohen, S. S., angioneural arthroses, 739
miliary tuberculosis of lungs and skin, 126
studies of experimental nephritis, 201
ulcer of stomach and duodenum, 175
uric acid in blood in gout, 397
Cole, R. I., multiple congenital osteochondromas, 253
studies on pneumonia, 606, 616
Collins, J., relationship of organic diseases of nervous system to Rigg's disease, 87, 93, 94
Colloidal gold reaction, 720
Conner, L. A., functions of the diaphragm, 29
Rigg's disease, 94
spontaneous rupture of spleen in typhoid fever, 103
typhus fever in United States, 86
x-ray examinations, 50
Cultural results in Hodgkin's disease, 226

Dental sepsis, 700
Diabetic acidosis, studies in, 469
Diaphragm, functions of, 16
Dilating esophageal strictures, 185
Diphtheria, circulatory failure in, 399
Disseminated miliary tuberculosis of lungs and skin, 117
Dochez, A. R., studies on pneumonia, 606
Dock, G., adherent pericardium and cardiolysis, 254, 257
antityphoid vaccination in the army, 467
pulmonary abscess, 308
Downes, W. A., spontaneous rupture of spleen in typhoid fever, 103

Ellis, A. W. M., syphilitic affections of nervous system, 258
Ellsworth, S. W., precautionary *x*-ray examinations, 44
Endocarditis, bacterial, 309
Esophageal strictures, 185
Exophthalmic goitre, 587, 595
thyroid gland in, 576

Fixation of stomach and intestines, 136
Fleisher, M. S., intravenous injections in animal and human cancer, 30
Flexner, S., epidemic poliomyelitis, 55, 68
mode of transmission of poliomyelitis, 80
serum anaphylaxis, 100
Ford, W. W., pasteurization of milk, 40, 43
Rigg's disease, 93
Friedenwald, J., ulcer of stomach and duodenum, 157, 175
Functions of the diaphragm and their diagnostic significance, 16
Fussell, M. H., antityphoid vaccination in the army, 467
pulmonary abscess, 307
ulcer of stomach and duodenum, 175

Gay, F. P., studies of the nature of biological specificity, 13
Goitre, exophthalmic, 587, 595
Gout, 739
uric acid in blood in, 387

Halsted, W. S., hypertrophy of thyroid gland, 127, 135
Hamilton, W. F., recurrent pneumonia, 422
Heart-beat in the dog, 545
Hemiplegias, pneumonic, 477
Heredity, with reference to carcinoma, 235
Herrick, J. B., benzol in treatment of leukemia, 224
secondary tumors of lung and pleura, 407
Hodgkin's disease, cultures in, 226
Hoover, C. F., bronchiectasis, 780
functions of the diaphragm and their diagnostic significance, 16, 29
hypertensive cardiovascular disease, 385
lesions of the nervous system, 738
syphilitic affections of nervous system, 274
Howard, C. P., bronchiectasis, 738, 780
Hypertensive cardiovascular disease, 333
Hypertrophy of thyroid gland, 127

Incidence of nephritis after scarlet fever, 194
Intravenous injections of various substances in animal and human cancer, 30

Jackson, H. hypertensive cardiovascular disease, 385
Janeway, T. C., diabetic acidosis, 475
hypertensive cardiovascular disease, 333, 386
rupture of spleen in typhoid fever, 116

Kinyoun, J. J., serum anaphylaxis, 101
Kober, G. M., antityphoid vaccination in the army, 466
Krause, A. K., pulmonary tuberculosis, 441

Landis, H. R. M., pulmonary abscess, 302
Leathes, J. B., bronchopneumonia, 440
diabetes acidosis, 476
Leukemia, benzol in treatment of, 202
Libman, E., pulmonary abscess, 307
subacute bacterial endocarditis, 309, 332
uric acid in blood in gout, 397
Liver, abscess of, 572
cirrhosis of, 497
Lobar form of bronchopneumonia, 430
Loeb, L., intravenous injections in animal and human cancer, 30
Longcope, W. T., cirrhosis of liver produced by chronic protein intoxication, 497
Lord, F. T., bronchiectasis, 779
bronchopneumonia, 439
pulmonary abscess, 308
tuberculosis, 448
Rigg's disease, 93
Lung and pleura, tumors of, 407
Lyon, H. N., intravenous injections in animal and human cancer, 30

McClurg, C. B., intravenous injections in animal and human cancer, 30
McCrae, J., incidence of nephritis after scarlet fever, 194, 197
McPhedran, A., adherent pericardium and cardiolysis, 256
benzol in treatment of leukemia, 226
hypertensive cardiovascular disease, 386
MacCallum, W. G., bronchiectasis, 779, 780
circulatory failure in diphtheria, 399
heart-beat in the dog, 571
hypertrophy of thyroid gland, 135
pulmonary tuberculosis, 448
Mason, V. R., tests for hepatic function and disease, 176
Matthews, S. A., venous blood-pressure, 490
Mechanism of circulatory failure in diphtheria, 399
Meltzer, dilating esophageal strictures, 193
fixation of stomach and intestines, 156
serum anaphylaxis, 101
syphilitic affections of nervous system, 274
ulcer of stomach and duodenum, 174
Miliary tuberculosis of lungs and skin, 117
Milk, observations on pasteurization of, 40
Miller, J. L., benzol in treatment of leukemia, 225
bronchopneumonia, 440
hypertensive cardiovascular disease, 385

Miller, J. L., incidence of nephritis after scarlet fever, 197
studies of experimental nephritis, 198
Mode of transmission of poliomyelitis, 69
Moody, A M., colloidal gold reaction in diagnosis of syphilitic and other lesions of the cerebrospinal nervous system, 720
Multiple congenital osteochondromas, 248

Nephritis, scarlet fever and, 194
studies of experimental, 198
Nervous system, syphilitic affections of, 258
Noguchi, H., epidemic poliomyelitis, 55
Norris, G. W., pulmonary abscess, 302, 308
Northrup, W. P., disseminated miliary tuberculosis of lungs and skin, 117, 126

Ochsner, A. J., exophthalmic goitre, 604
Opie, E. L., thrombosis and occlusion of lymphatics, 449
Osteoarthropathy, pulmonary, 275

Pararthroses, 739
Park, W. H., antityphoid vaccination in the army, 466
epidemic poliomyelitis, 68
observations on pasteurization of milk, 43
serum anaphylaxis, 95, 102
typhus fever in United States, 85
Pasteurization of milk, 40
Pearce, R. M., uric acid in blood in gout, 397
Peightal, T. C., tests for hepatic function and disease, 176
Periarthroses, 739
Phobia, 530
Plummer, H. S., dilating esophageal strictures, 192
exophthalmic goitre, 587, 604
Pneumonia, recurrent, 422
studies on, 606
Pneumonic hemiplegias, 477
Poliomyelitis, epidemic, 55
mode of transmission of, 69
Pratt, J. H., uric acid in blood in gout, 387, 398
Preble, R. B., abscess of liver following typhoid fever, 572
Precautionary *x*-ray examinations, 44
Primary infection with tubercle bacilli, 408
Prince, M., psychopathology of a case of phobia, 530
Pryor, J. C., pasteurization of milk, 40
Psychoanalytic movement, 513
Psychopathology of a case of phobia, 530
Pulmonary abscess, 302
osteoarthropathy, 275
tuberculosis, 441
Putnam, J. J., psychoanalytic movement, 513

Recurrent pneumonia, 422
Removal of diffusible substances from the circulating blood by means of dialysis, 51
Riesman, D., lobar form of bronchopneumonia, 430, 440
Rigg's disease, 87
Ringer, A. L., studies in diabetic acidosis, 469, 476
Robinson, G. C., heart-beat in the dog, 545
Rosenau, M. J., epidemic poliomyelitis, 68
mode of transmission of poliomyelitis, 69
observations on pasteurization of milk, 43
Rowntree, L. G., removal of diffusible substances from the circulating blood by means of dialysis, 51
Rudolf, R. D., bleeding in typhoid fever, 686
Rupture of spleen in typhoid fever, 103
Russell, F. F., antityphoid vaccination in the army, 457, 467

Sandford, A. H., exophthalmic goitre, 595
Scarlet fever, nephritis and, 194
Sepsis, dental, 700
Serum anaphylaxis, 95, 545
Sewall, H., hypertensive cardiovascular disease, 385
subacute bacterial endocarditis, 332
Sippy, B. W., colloidal gold reaction in diagnosis of syphilitic and other lesions of the cerebrospinal nervous system, 720, 738
dilating esophageal strictures, 185, 193
Smith, T., primary infection with tubercle bacilli, 421
Spleen, rupture of, in typhoid fever, 103
Stomach and duodenum, ulcer of, 157
and intestines, acquired fixation or displacement of, 136
Studies of experimental nephritis, 198
on the nature of biological specificity, 13
Syphilitic affections of nervous system, 258
Sweek, W. O., intravenous injections of animal and human cancer, 30
Swift, H. F., syphilitic affections of nervous system, 258, 274

Taylor, A. E., tests for hepatic function and disease, 184
Tests for hepatic function and disease under experimental conditions, 176
Thayer, W. S., antityphoid vaccination in the army, 466
hypertensive cardiovascular disease, 385
incidence of nephritis after scarlet fever, 197
ulcer of stomach and duodenum, 175
Thompson, W. H., typhus fever in United States, 85
Thrombosis and occlusion of lymphatics, 449
Thyroid gland, hypertrophy of, 127
in exophthalmic goitre, 576
Transmission of poliomyelitis, mode of, 69
Tubercle bacilli, primary infection with, 408
Tuberculosis, pulmonary, 441

Tumors of lung and pleura, 407
Turner, B. B., removal of diffusible substances from the circulating blood by means of dialysis, 51
Typhoid fever, abscess of liver following, 572
bleeding in, 686
rupture of spleen in, 103
Typhus fever in the United States, 81
Tyson, J., benzol in treatment of leukemia, 224

Ulcer of stomach and duodenum, 157
United States, typhus fever in, 81
Uric acid in blood in gout, 387
Urobilin, 617

Vaughan, V. C., antityphoid vaccination in the army, 466
exophthalmic goitre, 603
pneumonia, 616
studies on the nature of biological specificity, 15
Venous blood-pressure, 490

Warthin, A. C., heredity with reference to carcinoma, 35
Whipple, G. H., exophthalmic goitre, 604
tests for hepatic function and disease, 176, 184
Wilbur, R. L., urobilin, 617
Williams, F. H., precautionary *x*-ray examinations, 44, 50
Wilson, L. B., thyroid gland in exophthalmic goitre, 576, 604
Withington, C. F., pneumonic hemipleia, 477, 489
serum anaphylaxis, 101

X-ray examinations, precautionary, 44

Yates, J. L., cultural results in Hodgkin's disease, 226